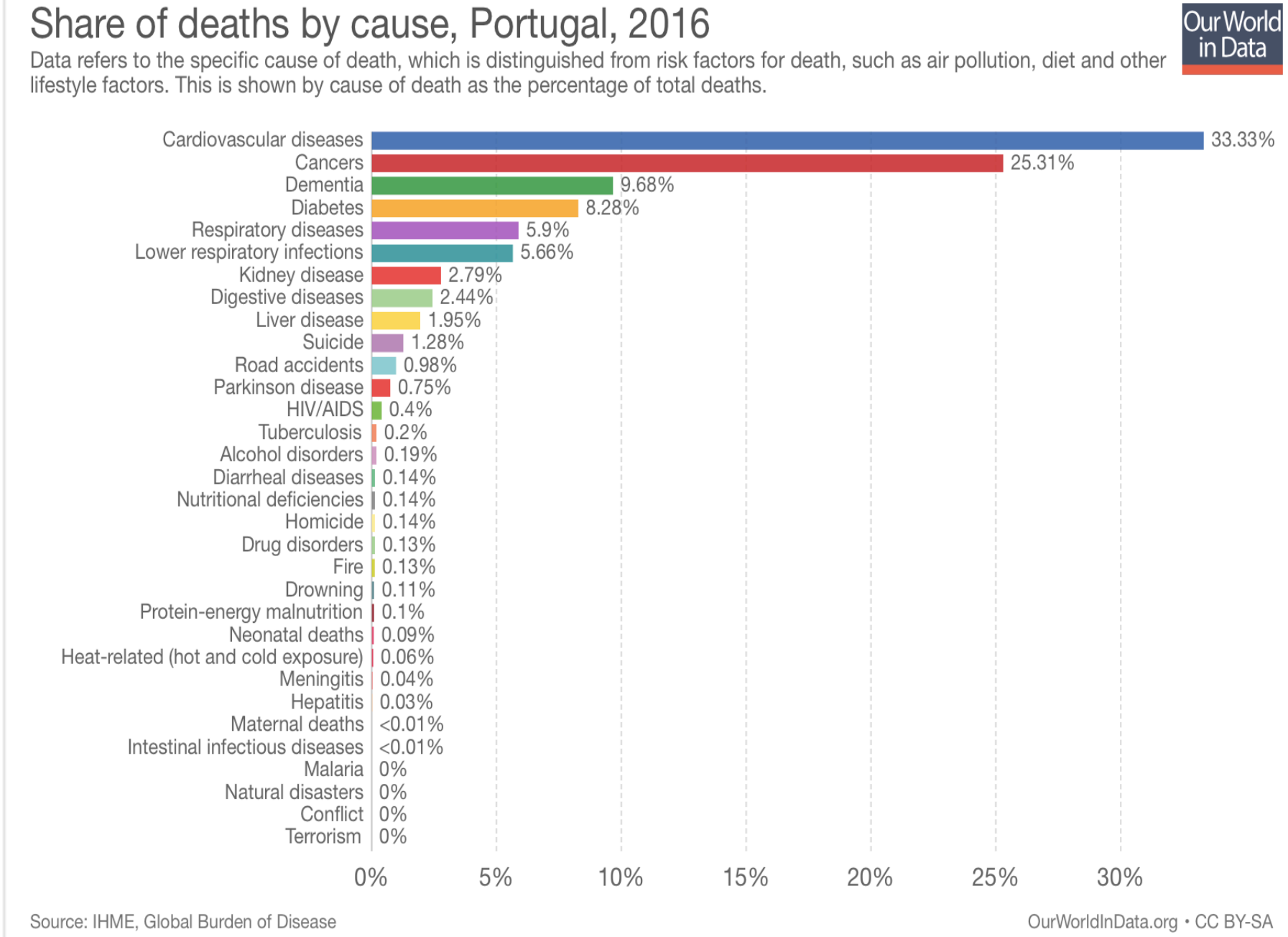
RADIOTERAPIA TORÁCICA E ENVOLVIMENTO CARDÍACO – AINDA HÁ RISCO?

Manuela Fiuza
CHLN-HSM/FML

Introdução


Share of deaths by cause, Portugal, 2016
Data refers to the specific cause of death, which is distinguished from risk factors for death, such as air pollution, diet and other lifestyle factors. This is shown by cause of death as the percentage of total deaths.
Our World in Data
Cardiovascular diseases 33.33%
Cancers 25.31%
Dementia 9.68%
Diabetes 8.28%
Respiratory diseases 5.9%
Lower respiratory infections 5.66%
Kidney disease 2.79%
Digestive diseases 2.44%
Liver disease 1.95%
Suicide 1.28%
Road accidents 0.98%
Parkinson disease 0.75%
HIV/AIDS 0.4%
Tuberculosis 0.2%
Alcohol disorders 0.19%
Diarrheal diseases 0.14%
Nutritional deficiencies 0.14%
Homicide 0.14%
Drug disorders 0.13%
Fire 0.13%
Drowning 0.11%
Protein-energy malnutrition 0.1%
Neonatal deaths 0.09%
Heat-related (hot and cold exposure) 0.06%
Meningitis 0.04%
Hepatitis 0.03%
Maternal deaths <0.01%
Intestinal infectious diseases <0.01%
Malaria 0%
Natural disasters 0%
Conflict 0%
Terrorism 0%
0%
5%
10%
15%
20%
25%
30%
Source: IHME, Global Burden of Disease
OurWorldInData.org • CC BY-SA

Introdução

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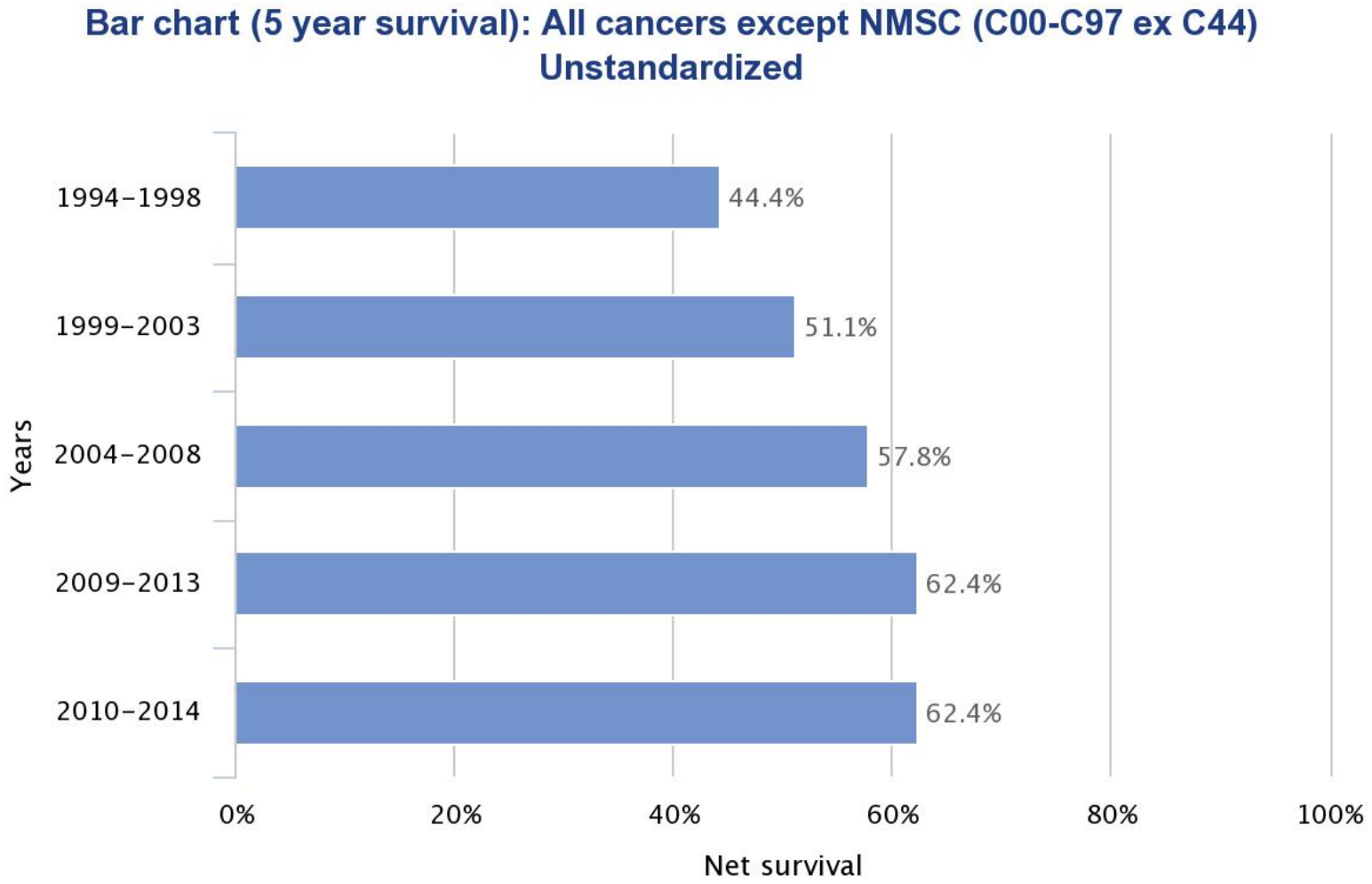
23 a 25 de Fevereiro 2018

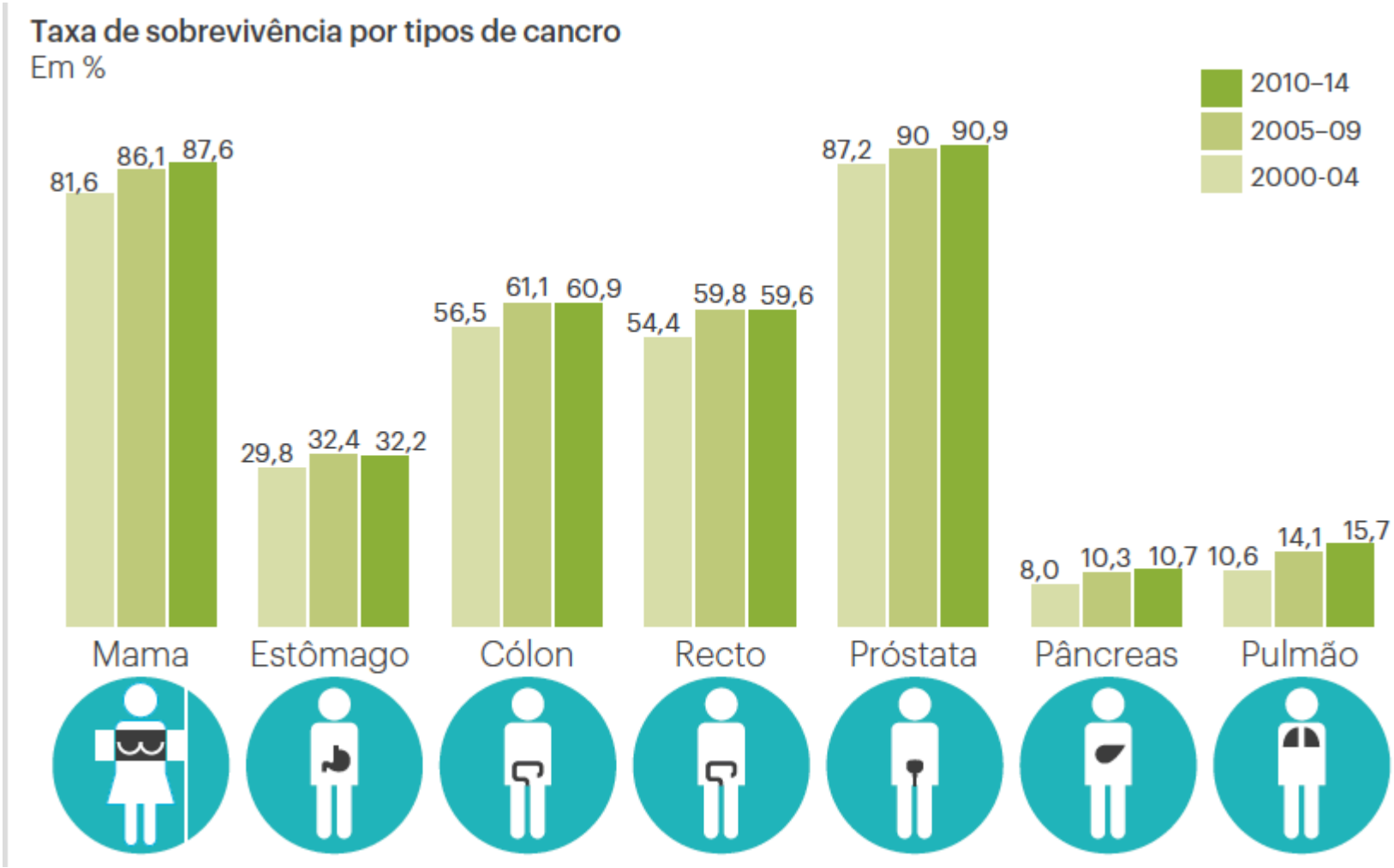
Taxa global de sobrevivência de cancro



Allemani C. et a. Concord 3.
www.thelancet.com Published online January 30, 2018 http://dx.doi.org/10.1016/S0140-6736(17)33326-3

Introdução

Portugal no Top 10 da sobrevivência do cancro



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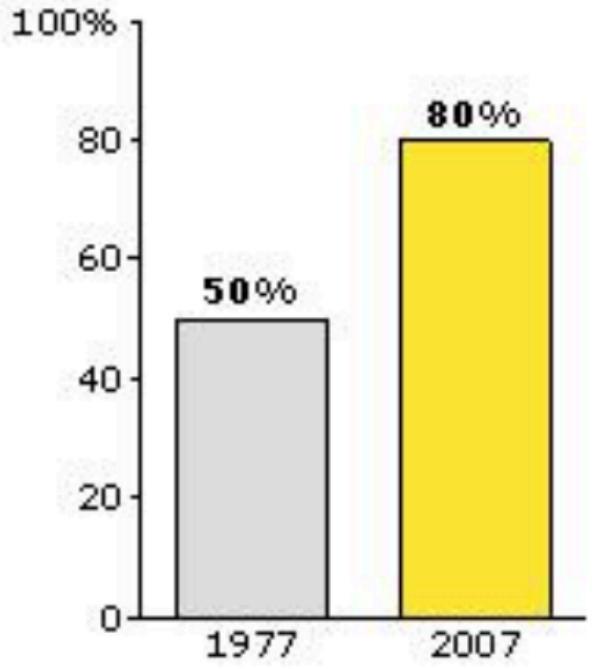
www.thelancet.com Published online January 30, 2018 http://dx.doi.org/10.1016/S0140-6736(17)33326-3

Introdução

Treatment efficacy has improved, but survivors pay a high price in side effects

Efficacy has improved...

5 year survival rates



...but side effects are increasingly damaging

- Secondary cancers
- Heart damage
- Lung damage
- Infertility
- Chronic hepatitis
- Alterations in growth and development
- Impaired cognitive abilities and psycho-social impact

Two-thirds of survivors experience at least one of these side effects

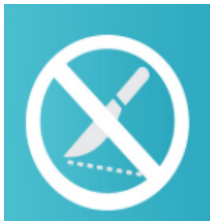
Div of Cancer control and pop. Sciences, NCI 2016

Introdução

Modalidades terapêuticas

CANCRO

- **CIRURGIA**
- **QUIMIOTERAPIA**
- **IMUNOTERAPIA**
- **RADIOTERAPIA**




Introdução

- Cerca de 15 milhões de novos casos/ano
- Cerca de 50% fazem radioterapia

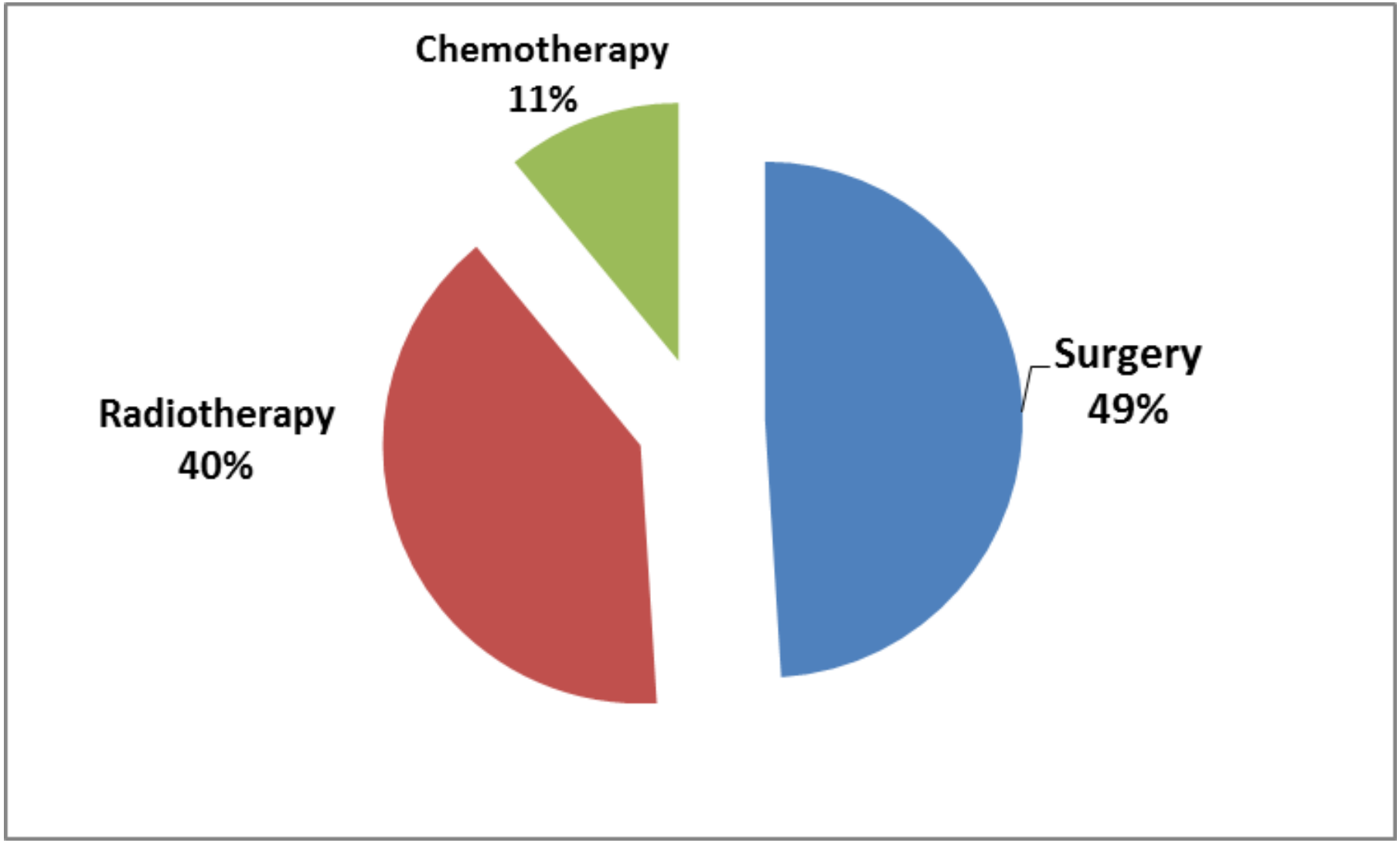
Tipos de Radioterapia

Radical: Para curar a doença

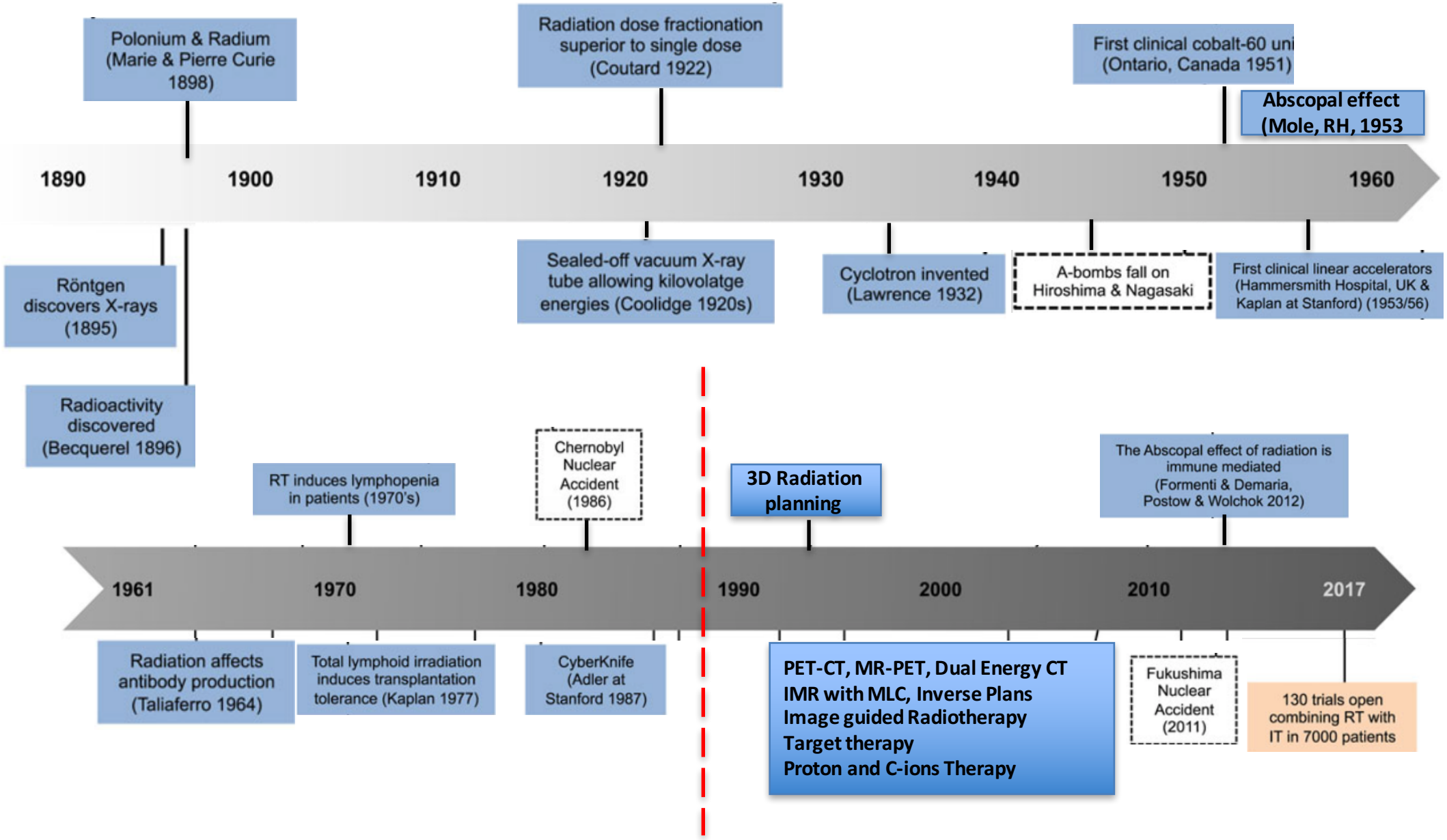
Paliativa: para aliviar sintomas

Introdução

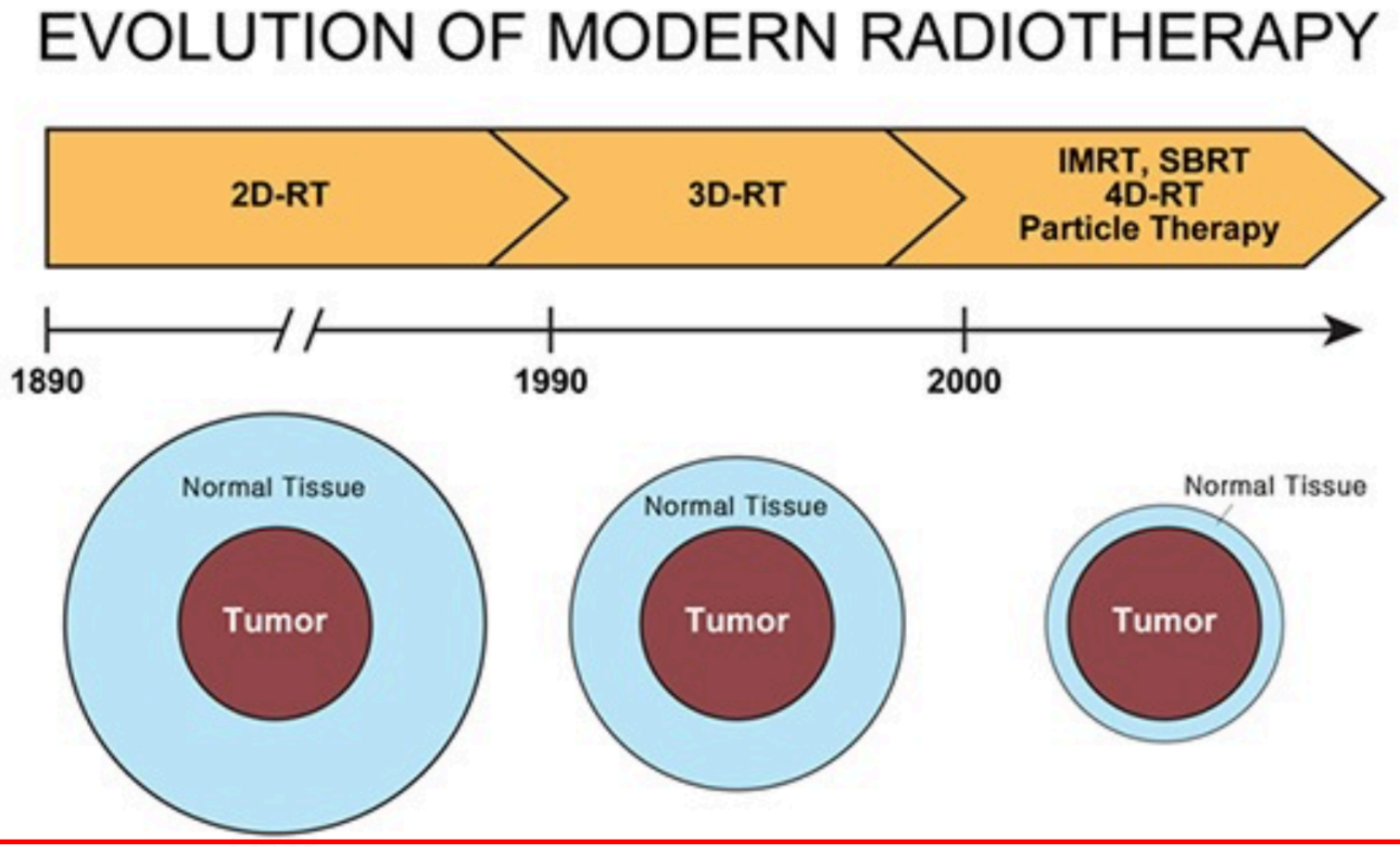
Taxas de cura



Milestones


Polonium & Radium (Marie & Pierre Curie 1898)
Radiation dose fractionation superior to single dose (Coutard 1922)
First clinical cobalt-60 uni (Ontario, Canada 1951)
Abscopal effect (Mole, RH, 1953
1890
1900
1910
1920
1930
1940
1950
1960
Röntgen discovers X-rays (1895)
Radioactivity discovered (Becquerel 1896)
Sealed-off vacuum X-ray tube allowing kilovolatge energies (Coolidge 1920s)
Cyclotron invented (Lawrence 1932)
A-bombs fall on Hiroshima & Nagasaki
First clinical linear accelerators (Hammersmith Hospital, UK & Kaplan at Stanford) (1953/56)
RT induces lymphopenia in patients (1970's)
Chernobyl Nuclear Accident (1986)
3D Radiation planning
The Abscopal effect of radiation is immune mediated (Formenti & Demaria, Postow & Wolchok 2012)
1961
1970
1980
1990
2000
2010
2017
Radiation affects antibody production (Taliaferro 1964)
Total lymphoid irradiation induces transplantation tolerance (Kaplan 1977)
CyberKnife (Adler at Stanford 1987)
PET-CT, MR-PET, Dual Energy CT
IMR with MLC, Inverse Plans
Image guided Radiotherapy
Target therapy
Proton and C-ions Therapy
Fukushima Nuclear Accident (2011)
130 trials open combining RT with IT in 7000 patients

Novas Modalidades



Modern radiotherapy is characterized by minimizing the volume of normal tissue being unnecessarily irradiated

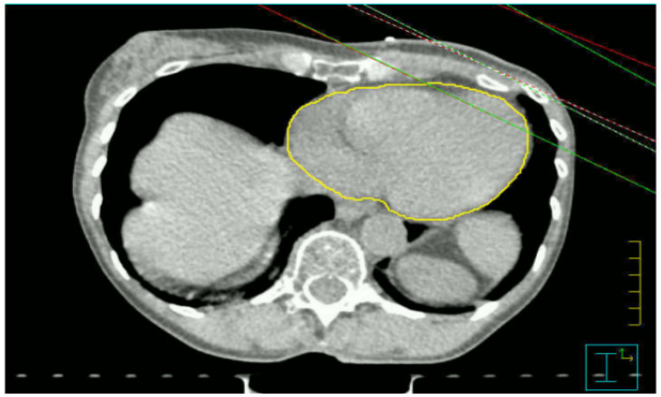
Evolving Clinical Cancer Radiotherapy: Concerns Regarding Normal Tissue Protection and Quality Assurance. Choi WH. J Korean Sci 2016; S75-S87

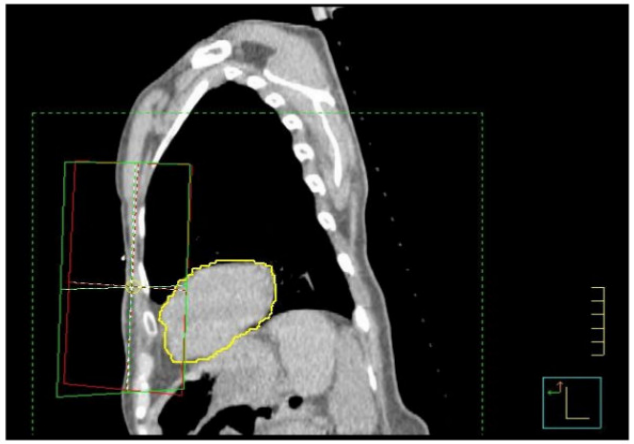
Novos Protocolos

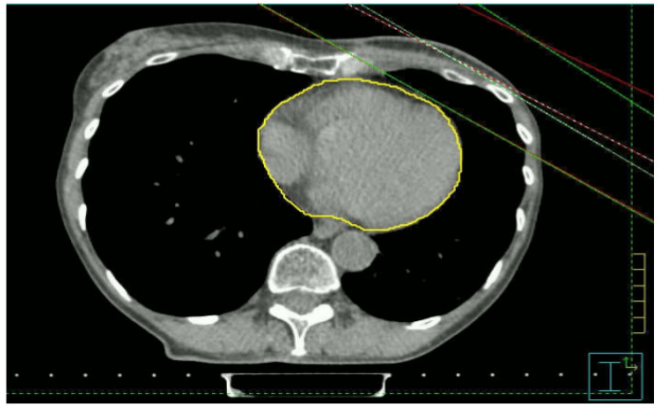
Real-time position (RPM)

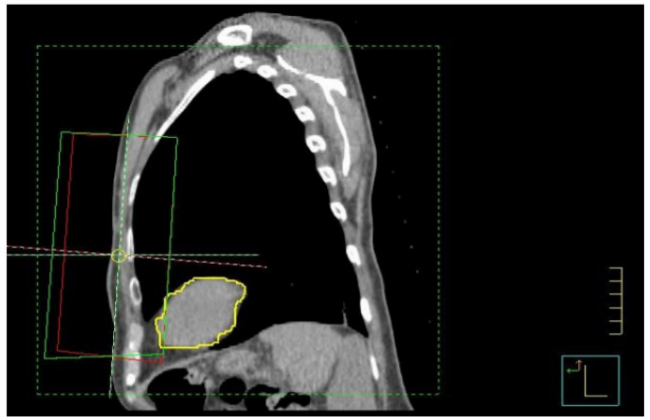
Active Breathing Coordinator (ABC)

Voluntary Breath-hold Technique



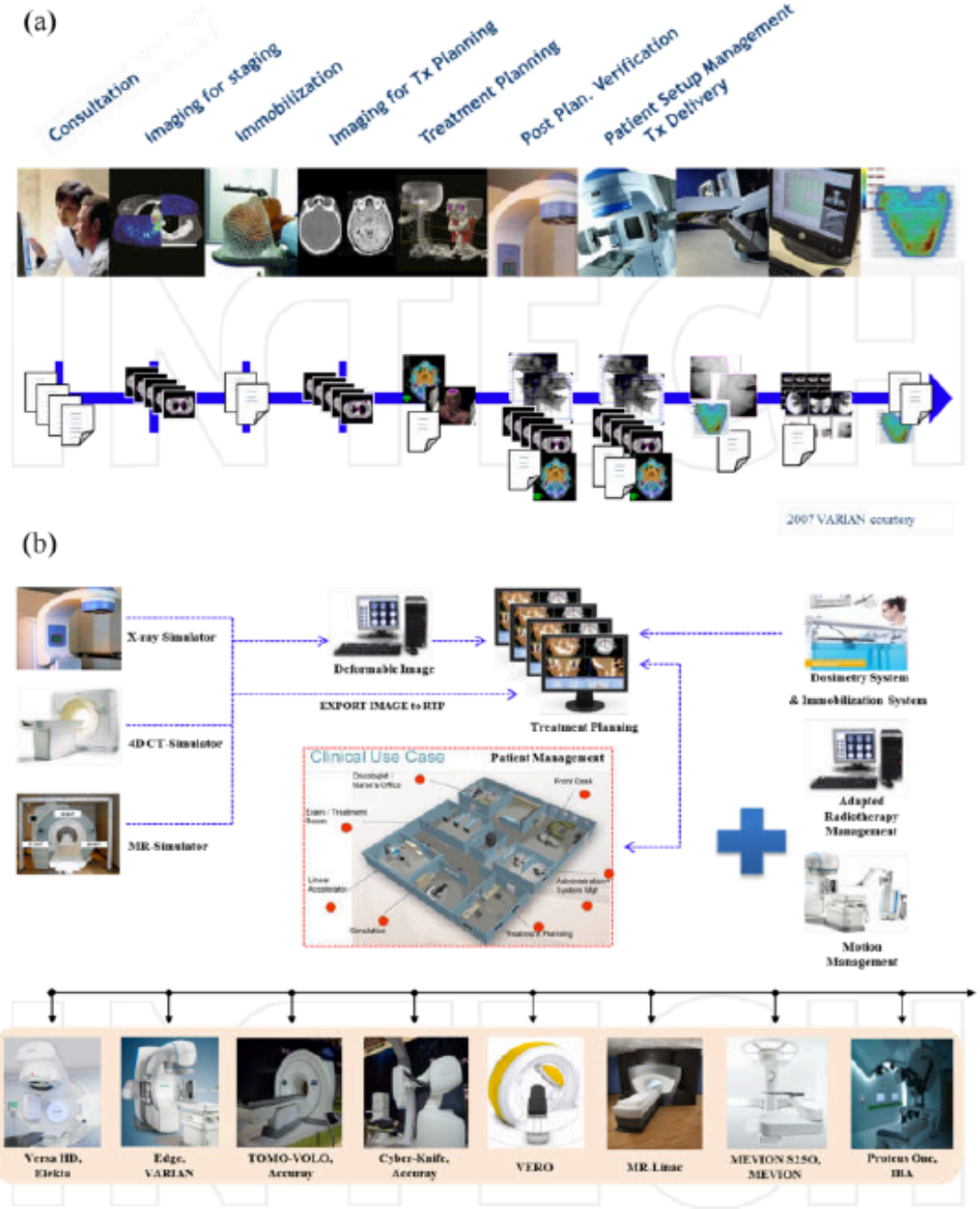






Latty D, *et al. J Med Radiat Sci*. 2015
Swanson T *et al .AM J Clin Oncol* 2013
Bartleett FR, et al *J Vis Exp.* 2014

Radioterapia XXI



Cardiotoxicidade

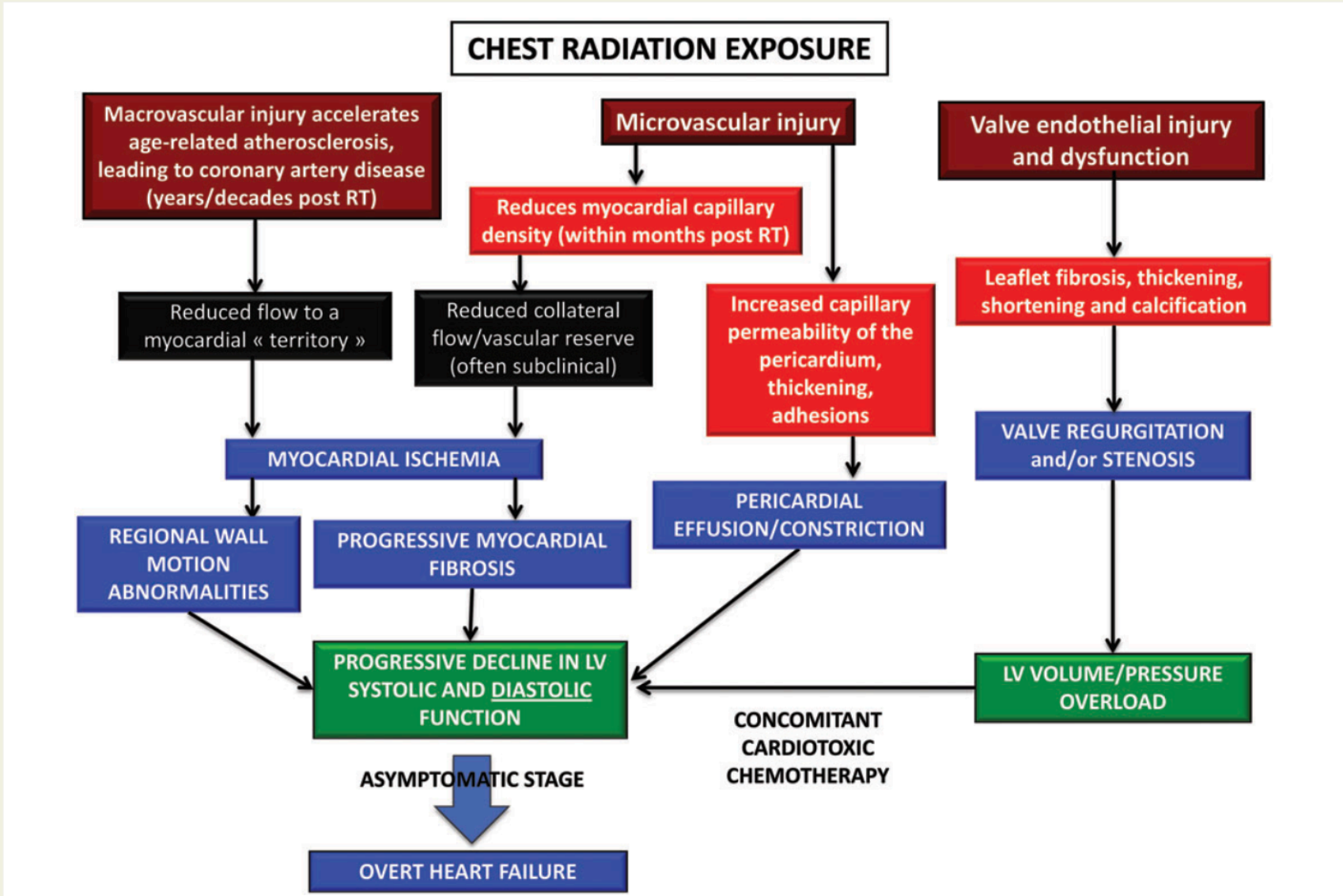


Figure 1 Pathophysiological manifestations of radiation-induced heart disease for different radiosensitive structures within the heart. LV: left ventricle; RT: radiotherapy.

Lancellotti P et al. Eur Heart J Cardiovascular Imaging (2013) 14, 721–740

Factores de risco

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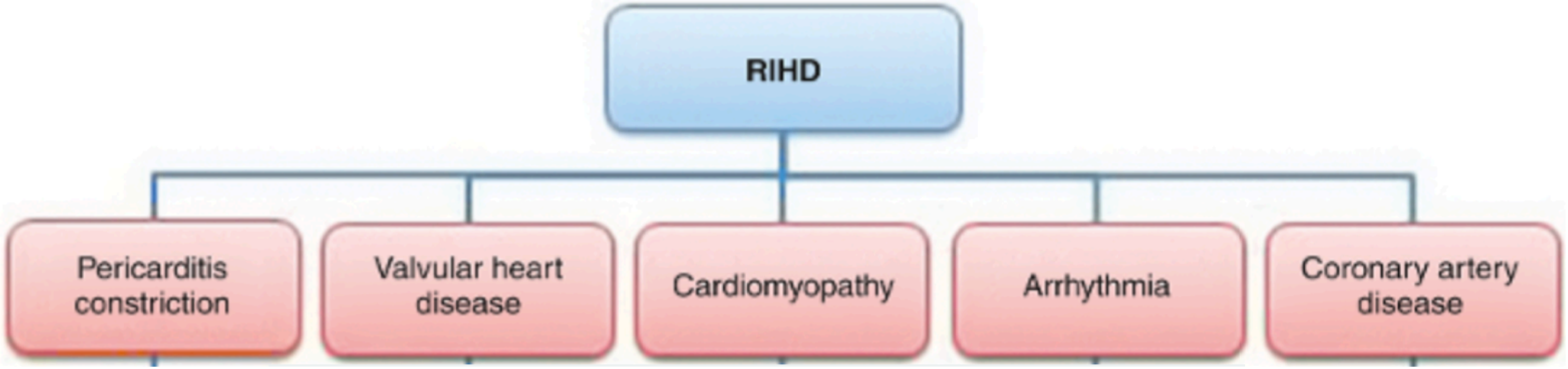
Table 2 **Risk factors of radiation-induced heart disease**

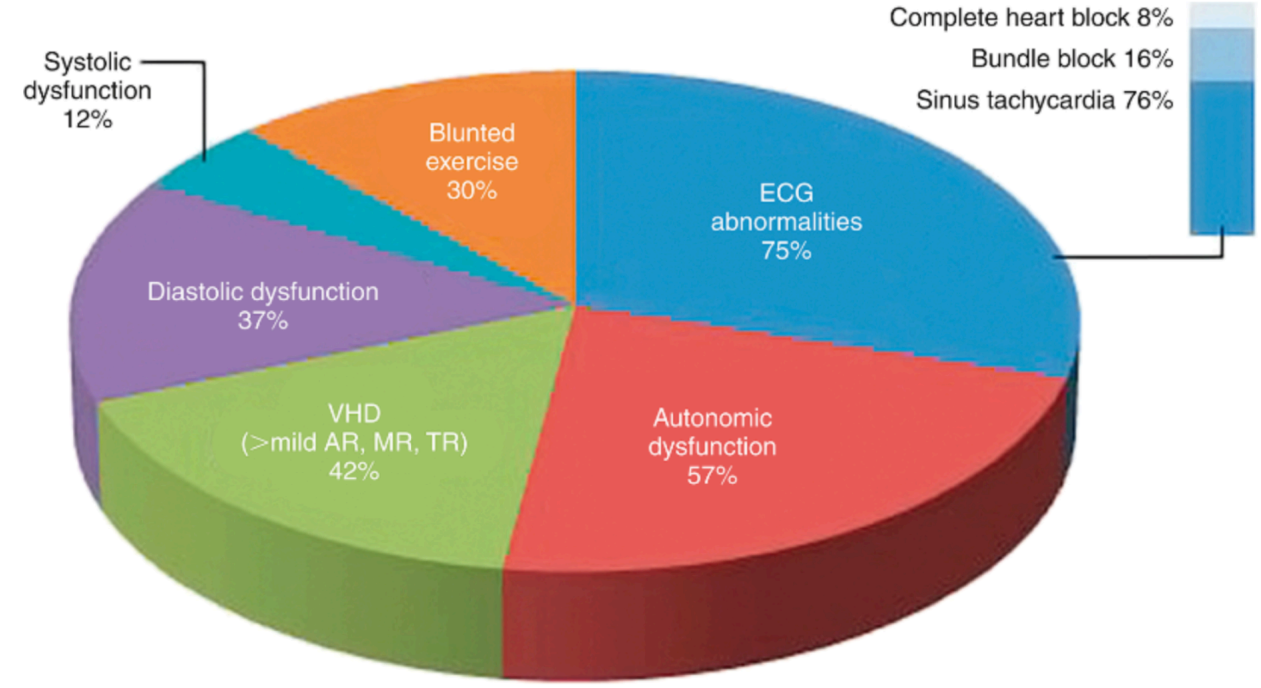
Anterior or left chest irradiation location
High cumulative dose of radiation (>30 Gy)
Younger patients (<50 years)
High dose of radiation fractions (>2 Gy/day)
Presence and extent of tumour in or next to the heart
Lack of shielding
Concomitant chemotherapy (the anthracyclines considerably increase the risk)
Cardiovascular risk factors (i.e. diabetes mellitus, smoking, overweight, ≥moderate hypertension, hypercholesterolaemia)
Pre-existing cardiovascular disease

High-risk patients definition: anterior or left-side chest irradiation with ≥1 risk factors for RIHD.

Lancellotti P et al. EHJ-Cardiovascular Imaging 2013; 14:721

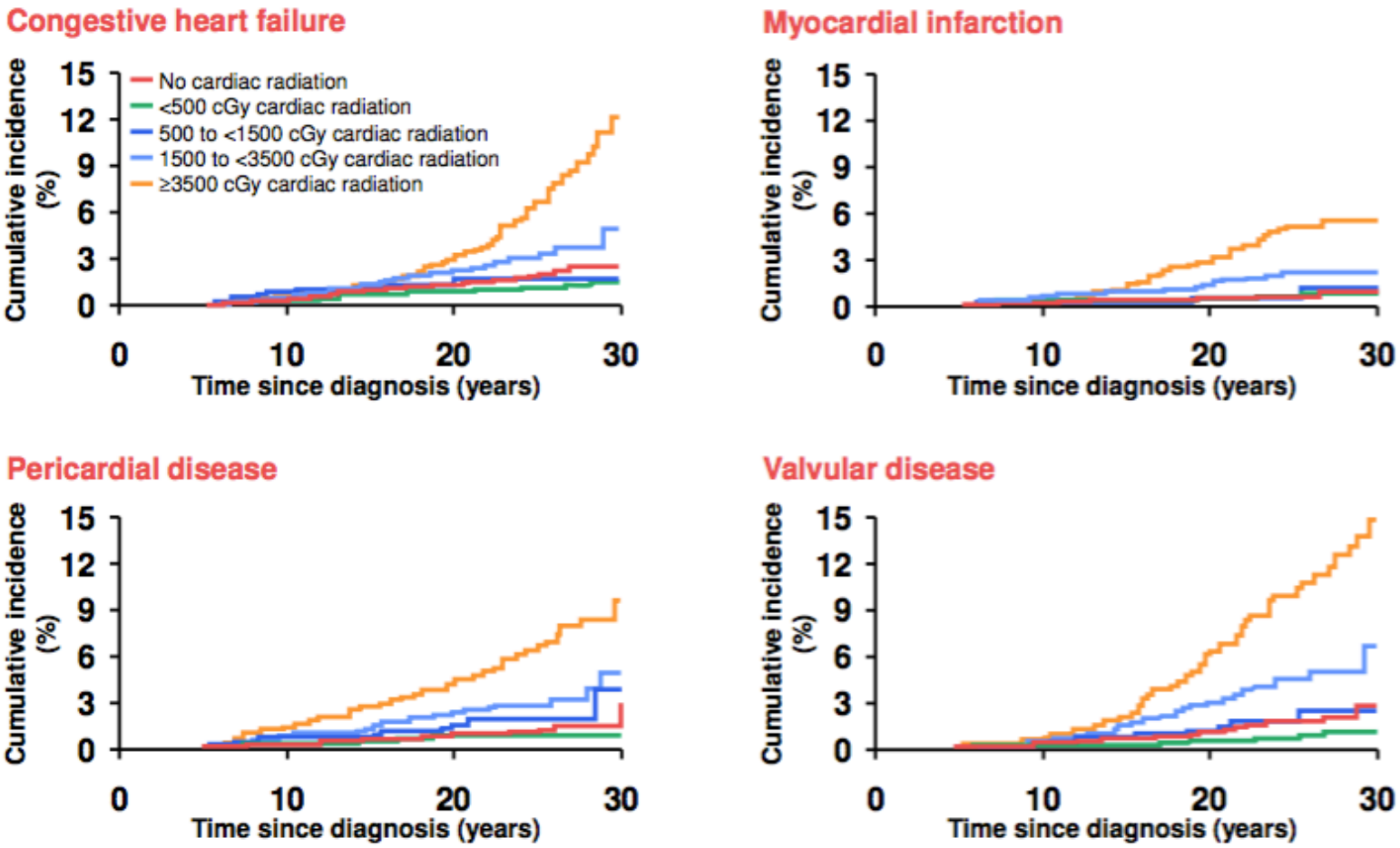
Cardiotoxicidade





Cardiotoxicidade

Radiation-induced Heart Disease

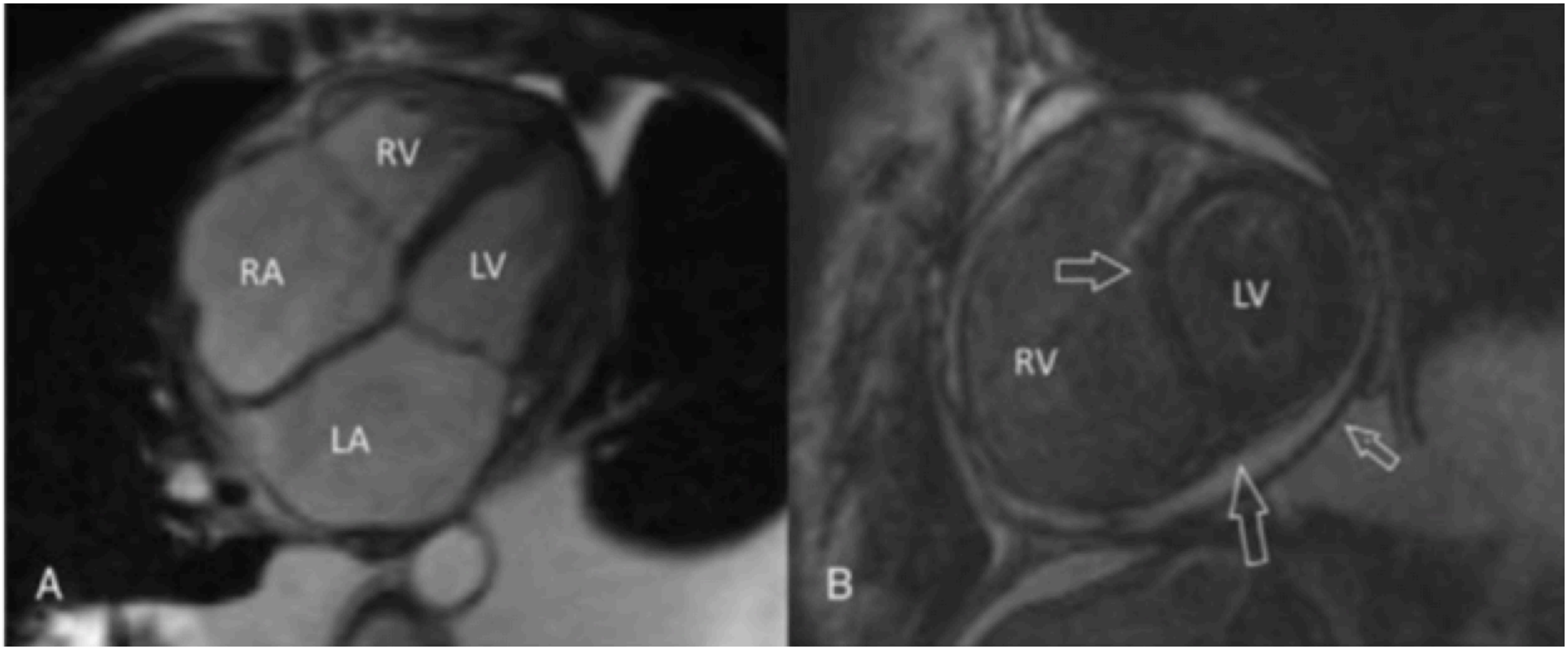


Groarke et al: Eur Heart J, 2013

Pericardial Disease

Prevalence: 6%–30%

Description: Pericarditis (acute or chronic), pericardial effusion, pericardial constriction.



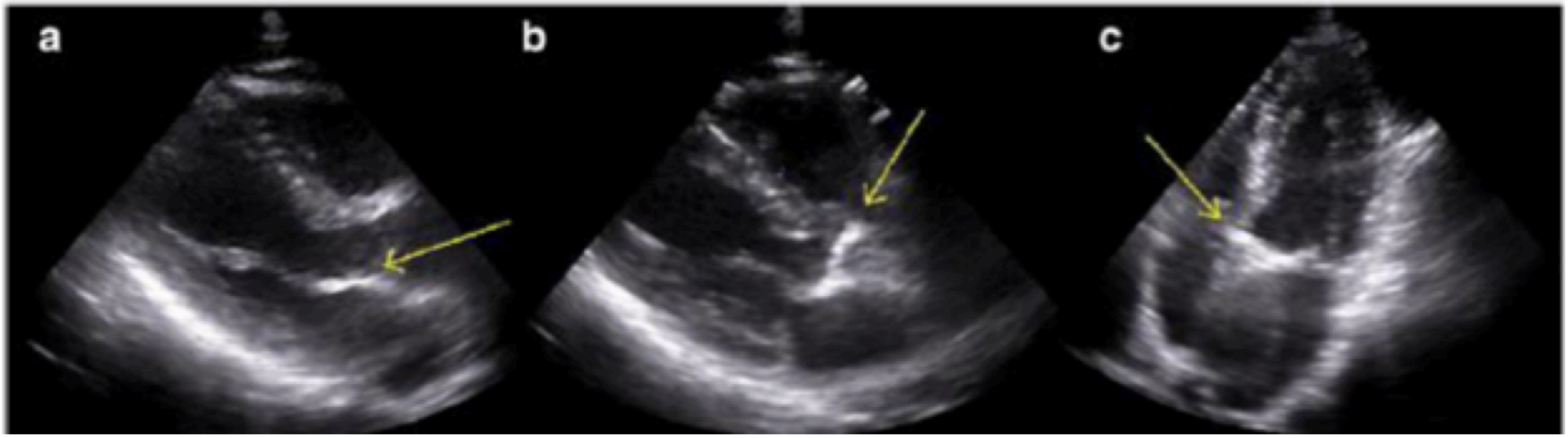
Valvular Heart Disease

Prevalence:

10 yrs: 26% AR, 39% MR, 16% TR, and 7% PR

20 yrs: 60% AR, 16% AS, 52% MR, 26% TR, and 12% PR

Calcification of the Mitral-aortic Junction

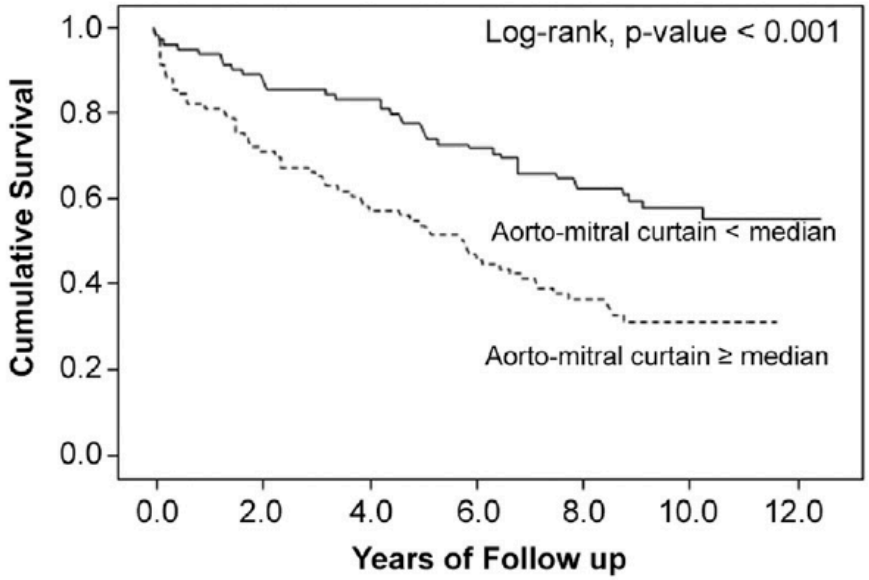


Increased Aorto-Mitral Curtain Thickness Independently Predicts Mortality in Patients With Radiation-Associated Cardiac Disease Undergoing Cardiac Surgery

Milind Y. Desai, MD, Willis Wu, MD, Ahmad Masri, MD, Zoran B. Popovic, MD, PhD, Shikhar Agarwal, MD, MPH, Nicholas G. Smedira, MD, Bruce W. Lytle, MD, and Brian P. Griffin, MD

Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio

(Ann Thorac Surg 2014;97:1348–55)



Number at Risk:							
Aorto-mitral curtain < median	86	75	72	62	54	24	1
Aorto-mitral curtain ≥ median	87	62	50	40	32	6	0

Cardiomyopathy

Prevalence: Up to 10%

Description: Diastolic dysfunction > systolic dysfunction; right ventricle > left ventricle.

Increased fibrosis in all 3 layers of the ventricular walls (epicardium, myocardium, and endocardium). May lead to restrictive cardiomyopathy, and rarely to systolic dysfunction.

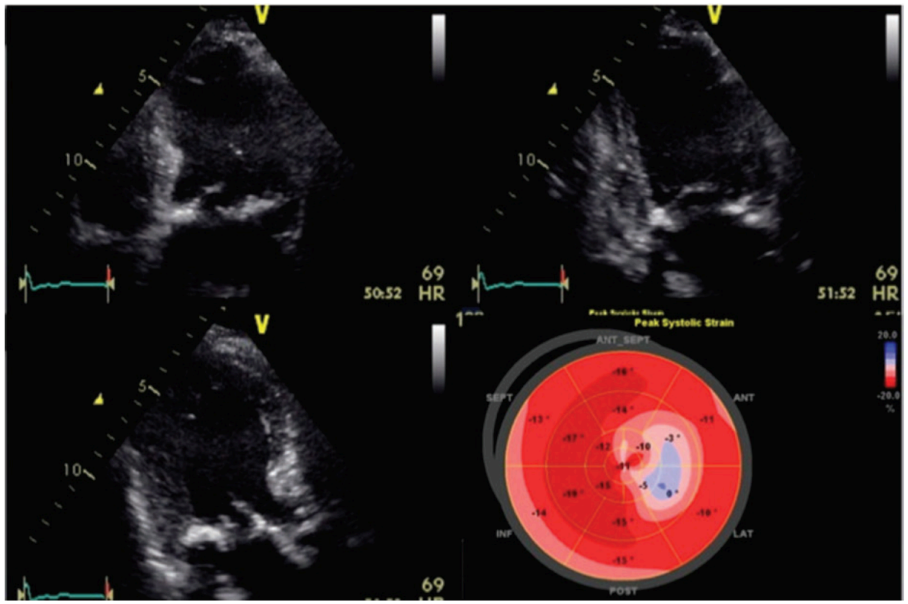


Figure 5 Echocardiography. Longitudinal left ventricular (LV) function assessed by 2D speckle tracking imaging of a patient with radiation-induced valvular heart disease and LV dysfunction. LV ejection fraction was normal while a Bull's eye plot of LV longitudinal strain (lower right panel) demonstrates impaired regional longitudinal function (light colours).

Lancellotti P et al. Eur Heart J Cardiovascular Imaging (2013) 14, 721–740

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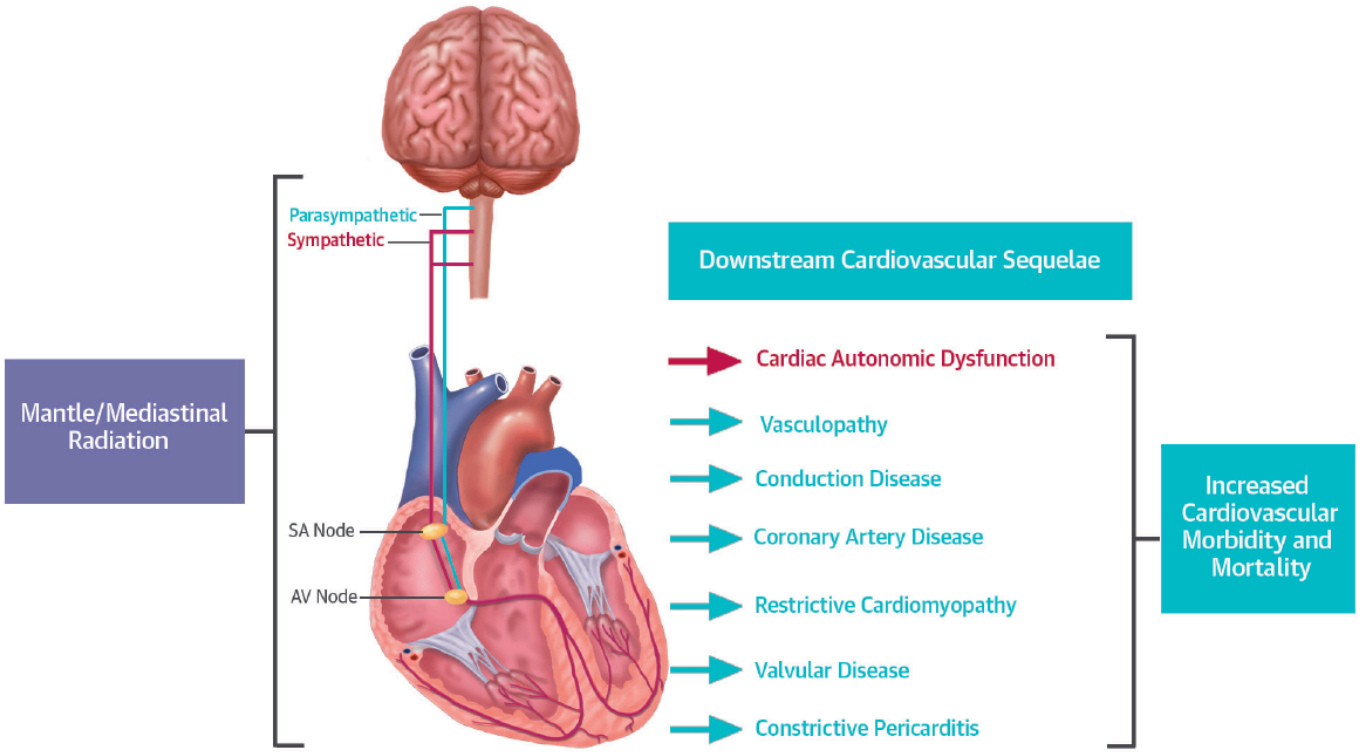
Abnormal Exercise Response in Long-Term Survivors of Hodgkin Lymphoma Treated With Thoracic Irradiation Evidence of Cardiac Autonomic Dysfunction and Impact on Outcomes

Groarke JD. J Am Coll Cardiol 2015;65:573–83

CENTRAL ILLUSTRATION Autonomic Dysfunction in Radiation Survivors



OUTCOME	ELEVATED RESTING HEART RATE*	ABNORMAL HEART RATE RECOVERY†
Exercise Duration	- 1.1 ± 0.3, p = 0.001	- 1.0 ± 0.4, p = 0.006
Mortality, HR (95% CI)	0.99 (0.40-2.45)	5.50 (1.97-15.36)

Relative to radiation patients without elevated resting heart rate*/with normal heart rate recovery†

Groarke, J.D. et al. J Am Coll Cardiol. 2015; 65(6):573-83.

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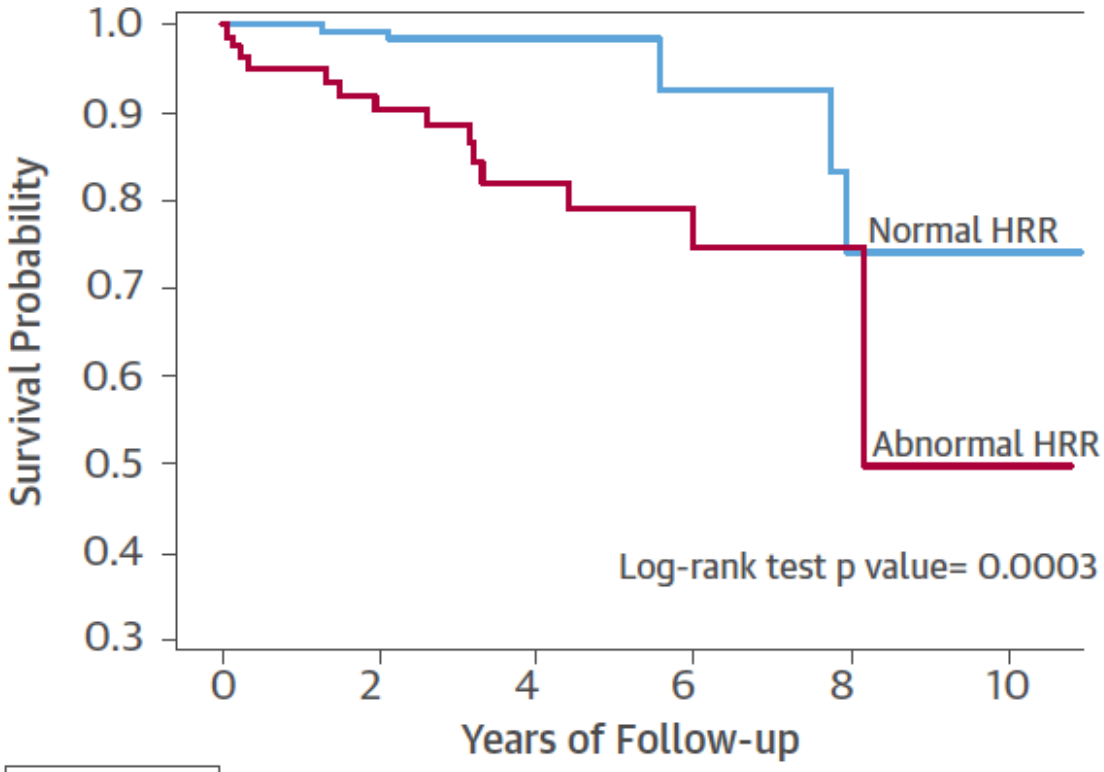
FIGURE 4 Kaplan-Meier Cumulative Survival Curves



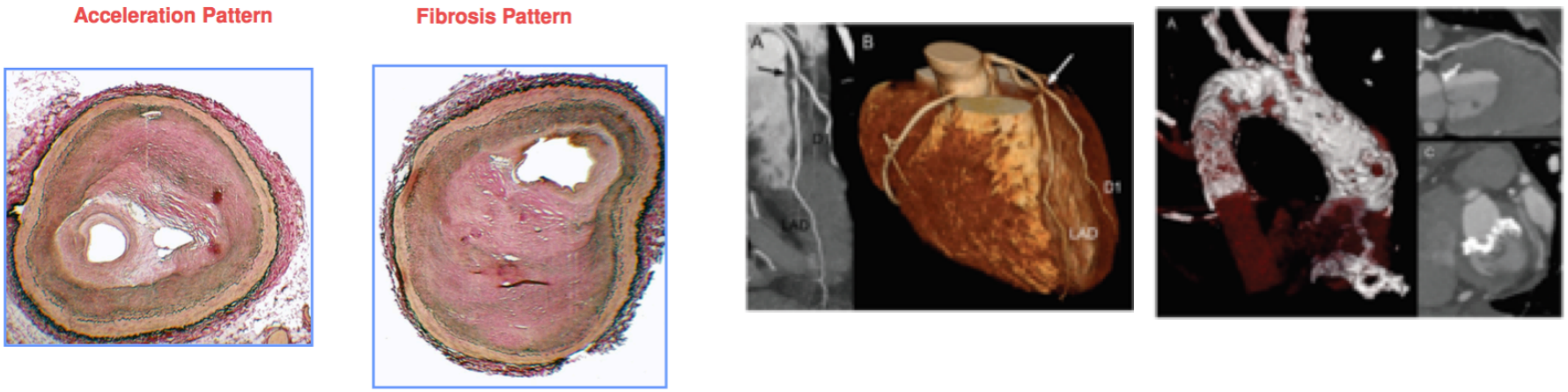
Patients at risk (n)						
Normal HRR	179	123	57	16	7	7
Abnormal HRR	84	53	31	18	3	3

Coronary Artery Disease

Prevalence: Up to 85%

Description: Due to epicardial coronary arteries and microcirculatory damage, and sustained inflammation. Usually occurs 10 yrs after radiation therapy. Involves the LM, ostial LAD, and RCA. Lesions are longer, concentric, and tubular.

Radiation-induced Coronary Artery Disease



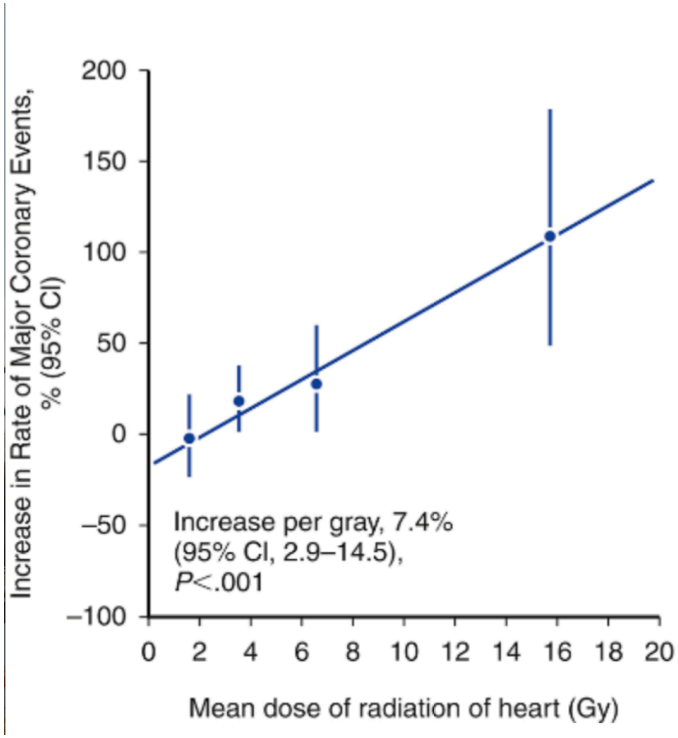
Lancellotti P et al. Eur Heart J Cardiovascular Imaging (2013) 14, 721–740

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Darby SC et al. N Engl J Med 2013;368:987-98.

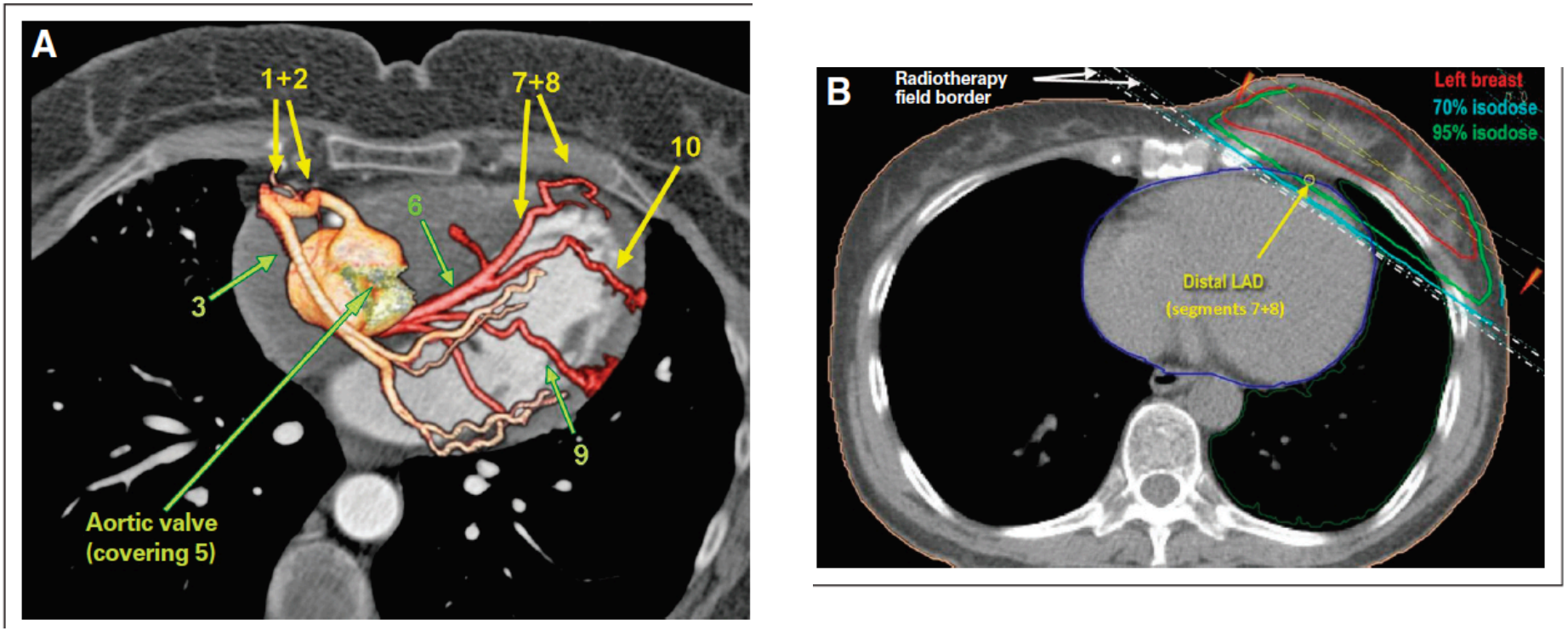
CONCLUSIONS

Exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease. The increase is proportional to the mean dose to the heart, begins within a few years after exposure, and continues for at least 20 years. Women with preexisting cardiac risk factors have greater absolute increases in risk from radiotherapy than other women. (Funded by Cancer Research UK and others.)



Distribution of Coronary Artery Stenosis After Radiation for Breast Cancer

Nilsson G. et al. J Clin Oncol 2012; 30:380-386.



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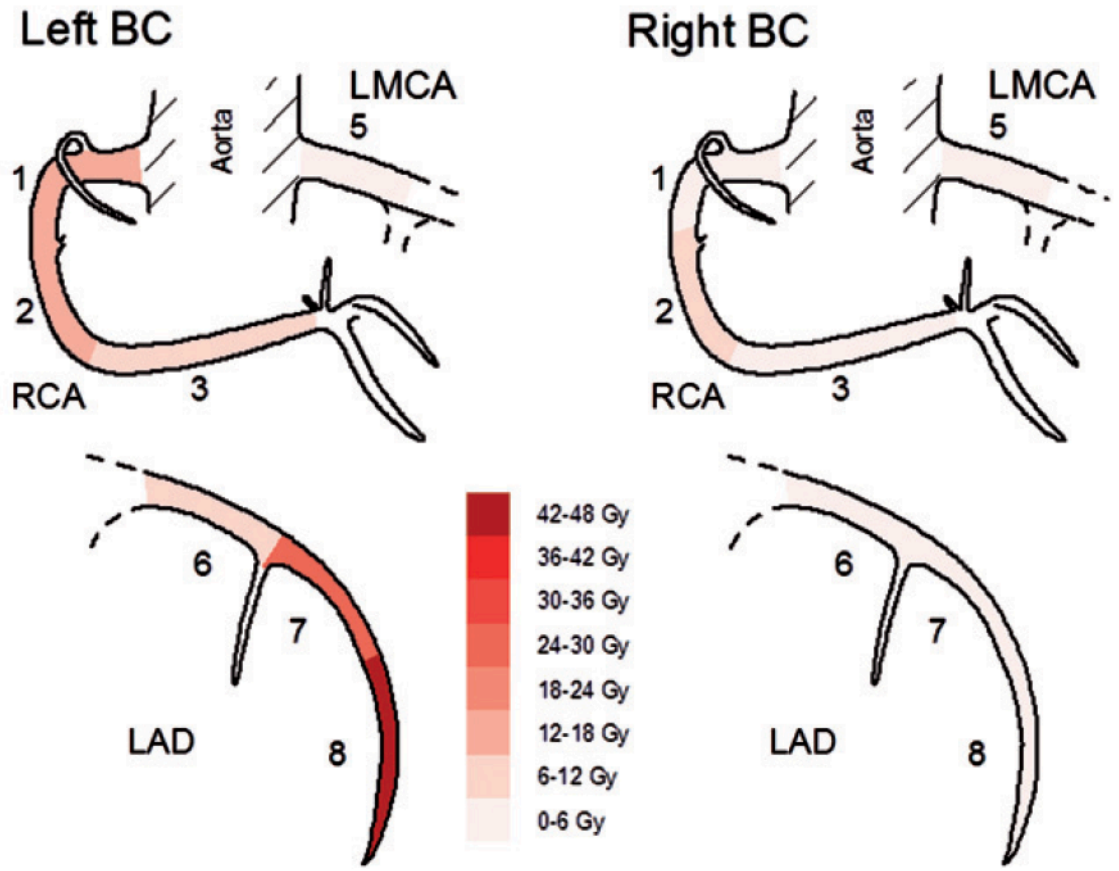
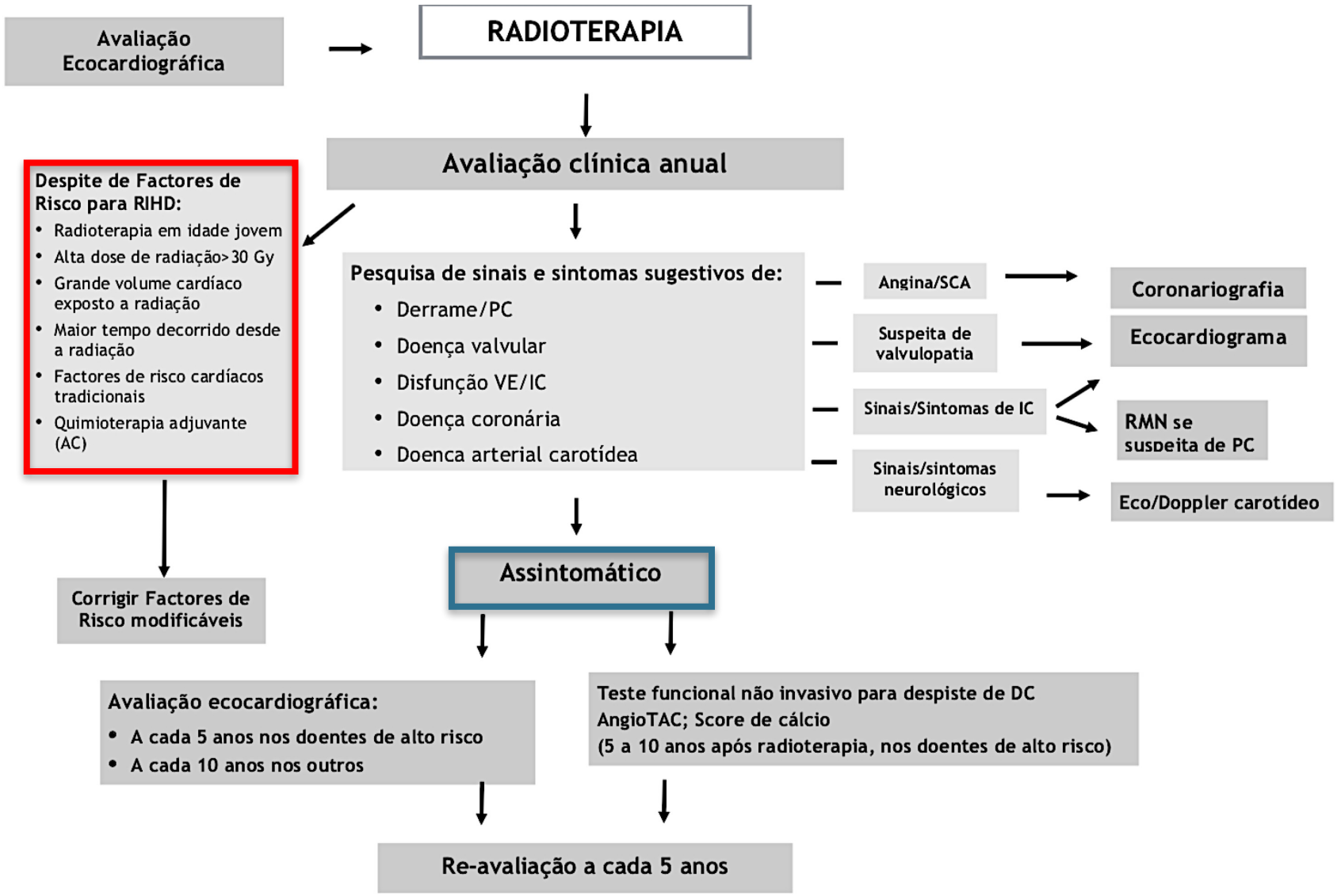


Figure 1. Segment-wise distribution of mean maximal radiation doses, of seven left- and eight right-sided women with breast cancer (BC). Gy: Gray; LMCA: left main coronary artery; LAD: left anterior descending artery; RCA: right coronary artery.

Avaliação e



RIHD: Cardiotoxicidade induzida pela radioterapia; AC: antraciclinas; PC: pericardite constritiva; DC; doença coronária; IC; insuficiência cardíaca
Definição de doentes de alto risco: irradiação torácica anterior ou à esquerda na presença de ≥1 para RIHD

MEDIRAD

Implications of Medical Low Dose Radiation Exposure

RESEARCH & INNOVATION
Horizon 2020

MEDIRAD EARLY-HEART: early detection of cardiovascular changes after RT for breast cancer

Teams and main researchers involved

IRSN / Clinique Pasteur, Toulouse (coordinator and investigating center):
Sophie Jacob, Epidemiologist

UMCG Groningen (investigating center):
Anne Crijn/Hans Langendijk , Radiation Oncologist
Rozemarijn Vliegenthart, Radiologist

TUM-MED, Munich (investigating center):
Stephanie Combs/ Daniela Schillings, Radiation Oncologist

CCUL, Lisbon (investigating center):
Manuela Fiuza, Cardiologist
Susana Constantino, Biologist

ICO, Girona (investigating center):
Arantxa Eraso / Feran Guedea, Radiation Oncologist

UPDescartes, Paris (Core center for reading Cardiac CT and Cardiac MR):
Elie Mousseaux, Radiologist

RESEARCH & INNOVATION
Horizon 2020

MEDIRAD EARLY-HEART:
early detection of cardiovascular changes after RT for breast cancer

MEDIRAD EARLY-HEART is a multicenter prospective cohort study that will include 250 females (left-sided and right-sided) BC patients treated with post-operative RT alone after primary breast conserving surgery.

Patients will be followed for 2 years after RT, based on cardiac imaging and circulating biomarkers

MEDIRAD EARLY-HEART

Introduction problem:

Breast cancer (BC) radiotherapy (RT) leads to coincidental radiation of the heart, resulting in increased risk of a variety of heart diseases.

Late cardiac complications have a major impact on quality of life and lead to subsequent morbidity and increased mortality.

Identifying BC patients with the highest-risk of radiation-induced cardiac complications is crucial for developing strategies for primary and secondary prevention

Little has been done on the relationship between dose distribution of the heart, in particular to different anatomical cardiac structures, during RT and early cardiovascular changes that may lead to cardiac complications.

Main study objectives:

The specific objective of the MEDIRAD-EARLY HEART study is to gain more insight in the relationship between radiation dose distributions to the heart, to different anatomical cardiac substructures, during RT and early cardiovascular changes (within two years).

To identify and validate most important cardiac imaging (echography, CT and MRI) and circulating biomarkers of radiation-induced cardiovascular changes arising in the first 2 years after breast cancer radiotherapy.

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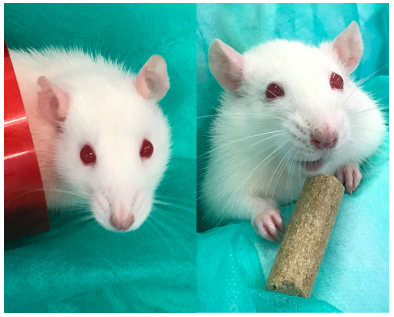
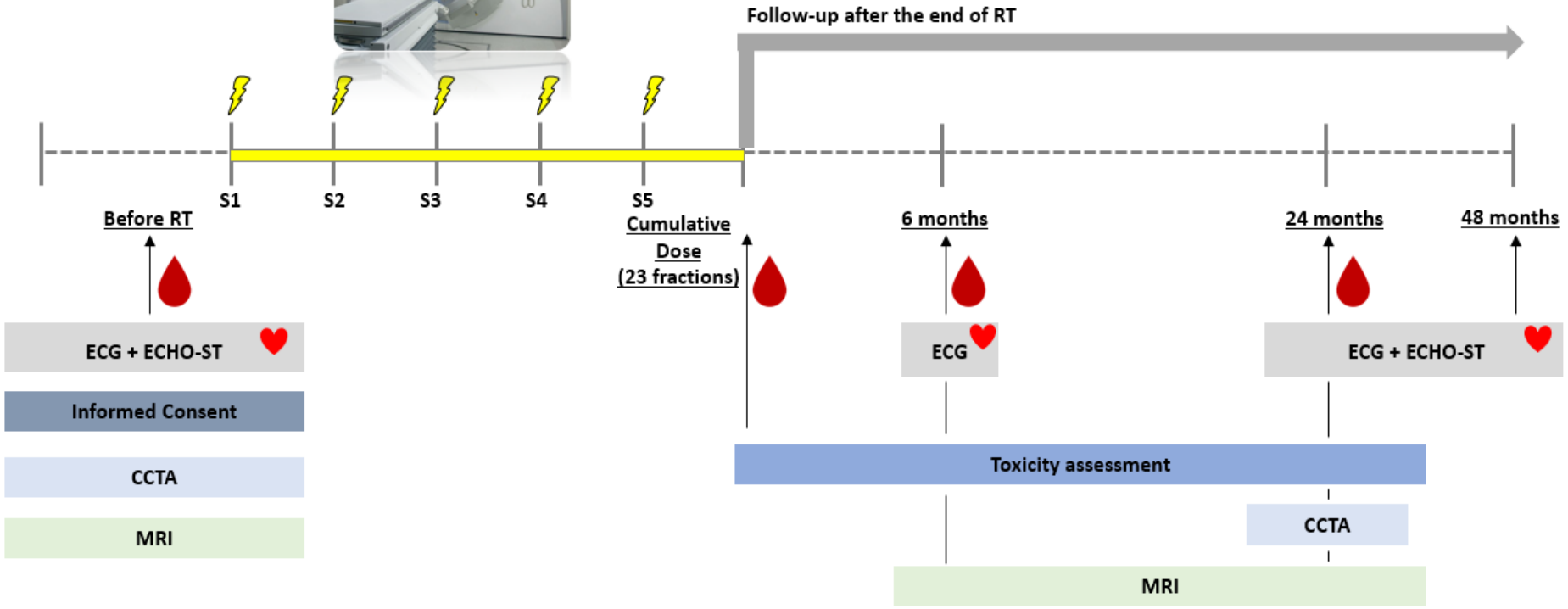
EARLY-HEART STUDY





Legend

Blood collection

Conclusões /Take home messages

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Risco de cardiotoxicidade se RT mediastino/torácica ≥30Gy
(Doença coronária, Ins. cardíaca, Pericardite, Doença valvular, Disritmias)

Maioria dos eventos cardíacos são tardios (15 – 20 anos)

Maioria estão descritos em doentes com longa sobrevivência
(Tumores da Mama e Linfoma de Hodgkin)

Avanços na RT para minimizar cardiotoxicidade
Definição dose de restrição/tolerância do coração
Uniformização de procedimentos (delimitação e relatório dosimétrico)
Melhoramento da tecnologia de → Exames de imagem,
→ Imobilização/posicionamento,
→ Planeamento/tratamento

Actualmente ainda há risco!
- A mais longo prazo? Mais atenuado?
- Como lidar com as situações – CABG/PCI/TAVI...
- Risco das associações terapêuticas

MEDIRAD EARLY-HEART

Study endpoints

Secondary endpoints

- Changes in myocardial function assessed by echocardiography 6 to 24 months after RT compared to baseline.
- Anatomical changes in coronary artery atherosclerosis (number of coronary segments containing any plaque/stenosis, and calcium score) by cardiac CT 24 months after RT compared with baseline. EP: 15% or greater changes.
- Myocardial changes by MRI 6 to 24 months after RT compared with baseline (morphology, function, tissue characterization by delayed enhancement and pre-/post-contrast T1 mapping). EP: increase of the mean pre-contrast T1 mapping value of at least 7%.
- Temporal changes in circulating biomarkers at the end of RT and 6 to 24 months after RT compared with baseline. EP: a statistically significant increase or decrease in each biomarker between time points.

MEDIRAD EARLY-HEART

Study endpoints

Primary endpoint

A mean decrease in Global Longitudinal Strain or Global Longitudinal Strain Rate, determined by cardiac ECHO-ST, of at least 2.5% between baseline and 24 months after RT.