Cardio-oncology Position Paper

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ESC CPG POSITION PAPER

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

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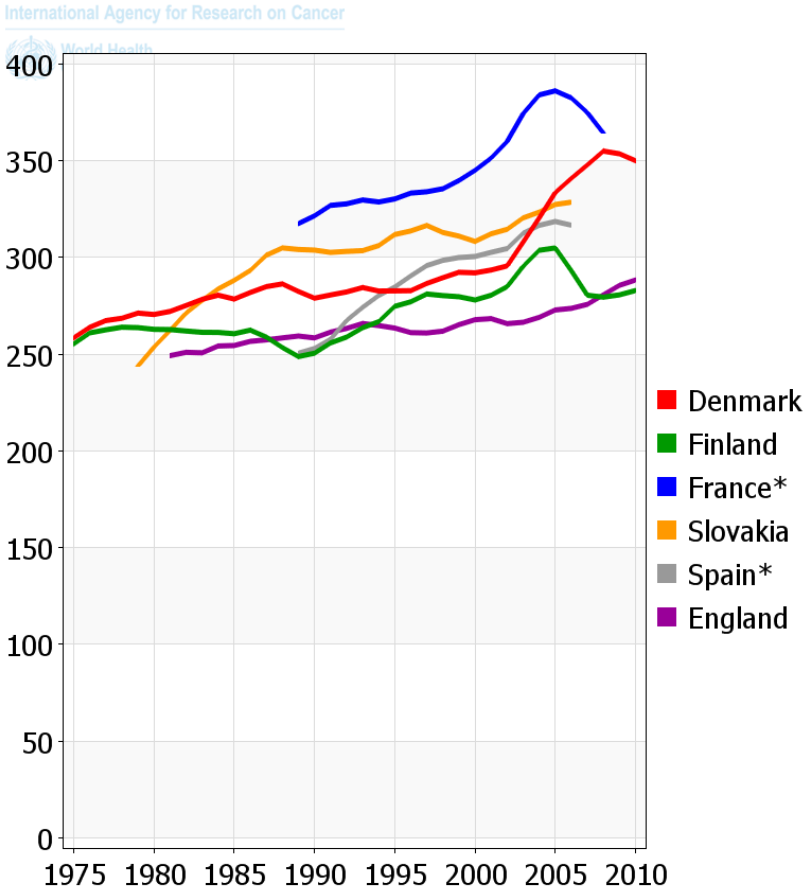
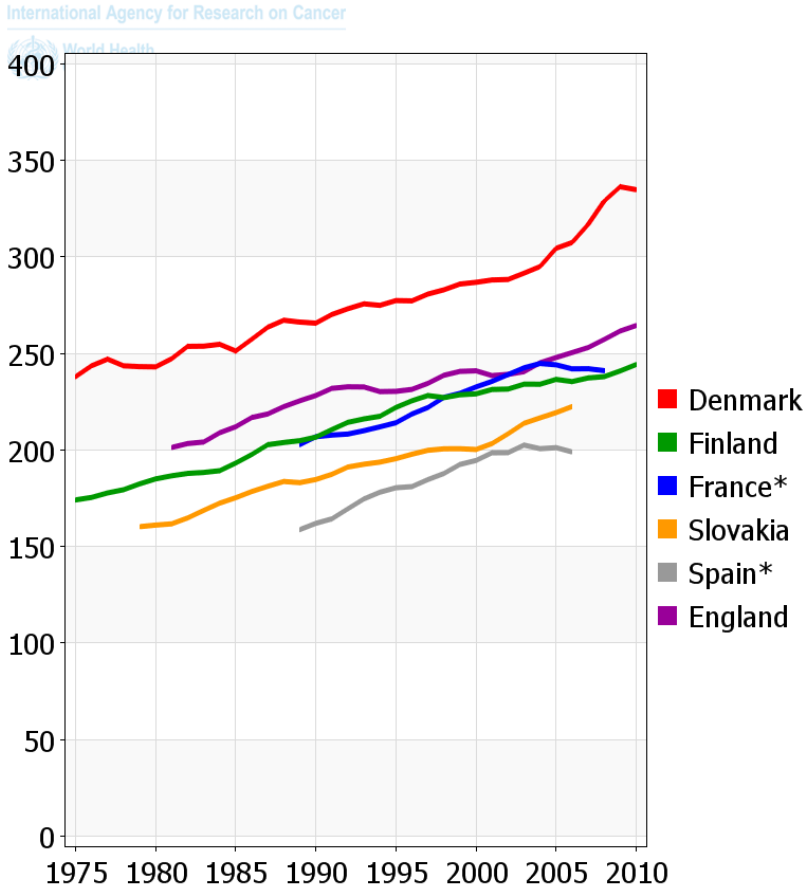
Why cardioncology?

- Ageing population - suffering of both cancer and CVD
- Increasing incidence of cancer patients
- Increasing incidence of CVD
- Incidence but also survival of cancer increasing
- Most survivors from cancer developing or dying from CVD
- Patients cured for cancer must not become heart failure patients
- Cancer therapy consequences may develop after many years from treatment
- The “sliding doors” concept: different treatment of patients if separate approach to care by oncologists or cardiologists – best treatment if cardiologists and oncologists interact

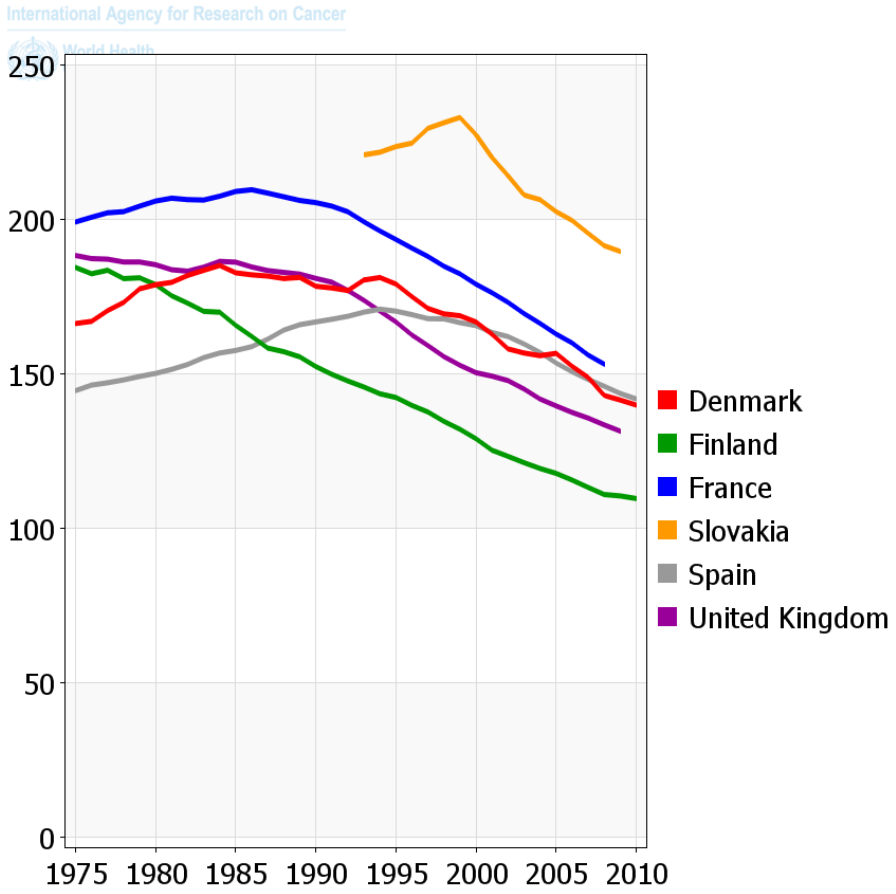
Trends in incidence of cancer in selected European countries - males



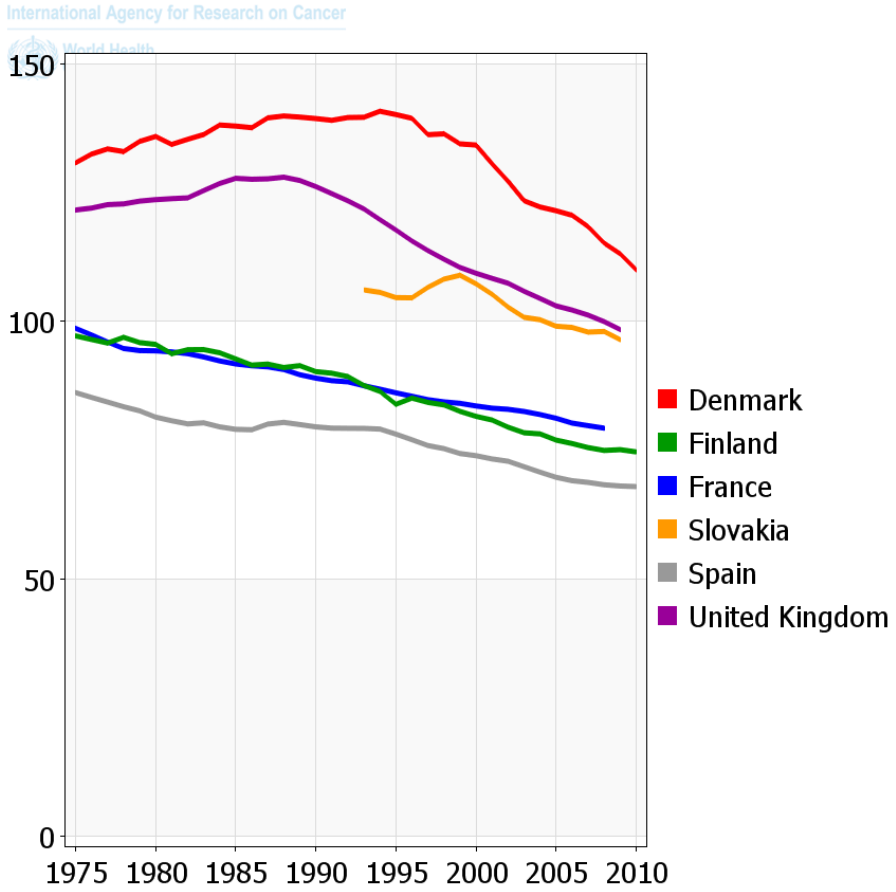
Trends in incidence of cancer in selected European countries - females



Trends in mortality of cancer in selected European countries - males



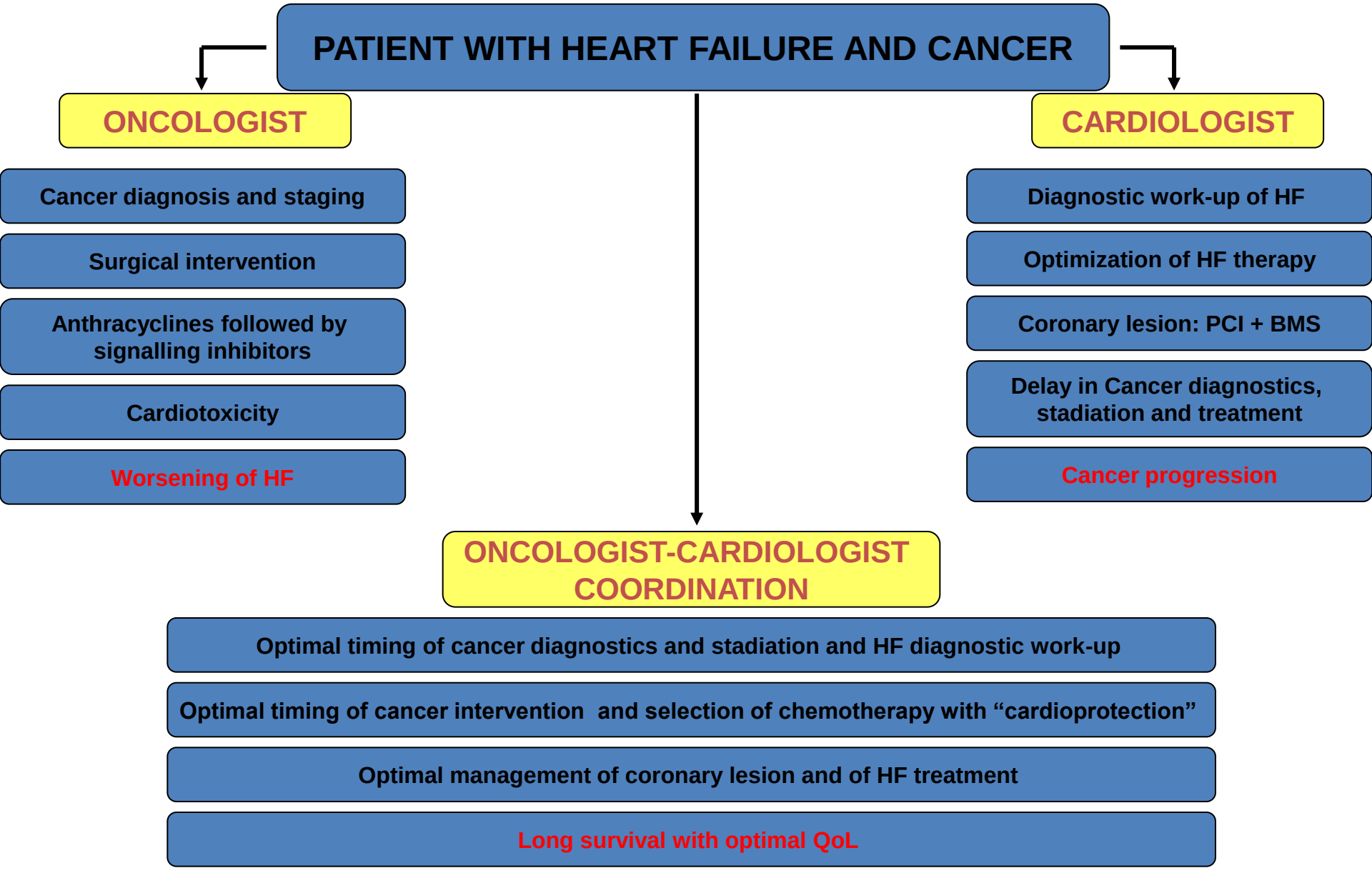
Trends in mortality of cancer in selected European countries - females



Relative five year survival (%) in Europe

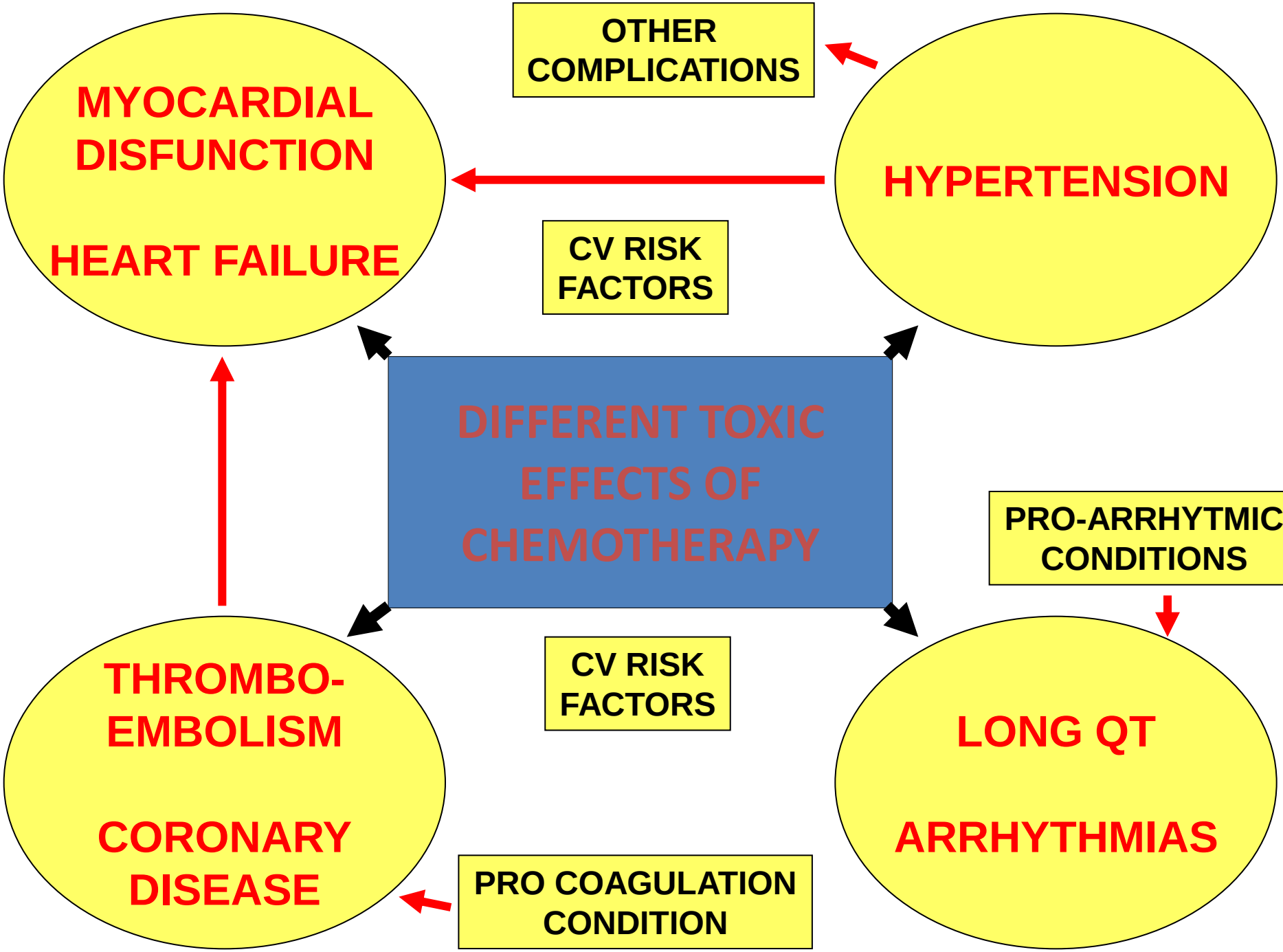
Cancers site	Relative survival	Proportion of cases
Lip, testis, thyroid, malignant melanoma, Hodgkin's lymphoma	> 80%	4%
Breast, prostate, bladder, cervix, uterus, larynx	60-79%	30%
Colon, rectum, kidney, non-Hodgkin lymphoma	40-59%	20%
Stomach, ovarian cancer, multiple myeloma	20-39%	10%
Lung, pancreas, oesophagus, brain, liver	< 20%	25%

The “SLIDING DOORS” Concept



Physiopathology and toxic Heart effects of CT drugs – General Principles

- Type I toxicity (cell necrosis - permanent cardiac damage)
- Type II toxicity (cell dysfunction - reversible cardiac damage)
- Potentiation of toxic effect by un-correct timing of association of type I and II drugs
- Shift from high doses chemotherapy in advanced stages of cancer to modulated chemotherapy with combinations of different agents (type I and II), lower doses and prolonged administration
- Shift from prolonging survival to side effects and QoL
- Paediatric and Older patients
- Not only Heart Failure


OTHER COMPLICATIONS
MYOCARDIAL DISFUNCTION
HEART FAILURE
HYPERTENSION
CV RISK FACTORS
DIFFERENT TOXIC EFFECTS OF CHEMOTHERAPY
PRO-ARRHYTMIC CONDITIONS
CV RISK FACTORS
THROMBO-EMBOLISM
CORONARY DISEASE
LONG QT
ARRHYTHMIAS
PRO COAGULATION CONDITION

Relationship cancer therapy – cardiovascular diseases

- Myocardial Dysfunction and Heart Failure (HF)
- Coronary Artery Disease (CAD)
- Valvular Heart Disease (VHD)
- Arrhythmias – LQT acquired
- Arterial Hypertension
- Thromboembolic Disease (TE)
- Peripheral Vascular Disease (PAD) and stroke
- Pulmonary Hypertension (PAH)
- Pericarditis

Myocardial Dysfunction and Heart Failure

- Strict control of cardiovascular risk factors
- LVEF assessment before and periodically during CT – same imaging method with good quality
- Lower limit of LVEF < 50%
- If reduction of LVEF > 10% but not under the lower limits repeat assessment during and shortly after CT
- If reduction of LVEF > 10% under the lower limit : ACE-Is (or ARBs) + Beta-Blockers to prevent further LV dysfunction
- ACE-Is (or ARBs) + B-Blockers in symptomatic HF or asymptomatic LV dysfunction

Risk Factors for cardiotoxicity following anthracyclines

- Cumulative dose
- Female sex
- Age
  - **>65 years old**
  - **Paediatric population (<18 years)**
- Renal failure
- Concomitant or previous radiation therapy involving the heart
- Concomitant chemotherapy
  - **alkylating or antimicrotubule agents**
  - **immuno- and targeted therapies**
- Pre-existing conditions
  - **Cardiac diseases associating increased wall stress**
  - **Arterial hypertension**
  - **Genetic factors**

Myocardial Dysfunction and Heart Failure

Table 6 Proposed diagnostic tools for the detection of cardiotoxicity

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: **- 3D-based LVEF** **- 2D Simpson's LVEF** **- GLS**	• LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. • GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.	• Wide availability. • Lack of radiation. • Assessment of haemodynamics and other cardiac structures.	• Inter-observer variability. • Image quality. • GLS: inter-vendor variability, technical requirements.
Nuclear cardiac imaging (MUGA)	• >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity.	• Reproducibility.	• Cumulative radiation exposure. • Limited structural and functional information on other cardiac structures.
Cardiac magnetic resonance	• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.	• Accuracy, reproducibility. • Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.	• Limited availability. • Patient's adaptation (claustrophobia, breath hold, long acquisition times).
Cardiac biomarkers: **- Troponin I** **- High-sensitivity Troponin I** **- BNP** **- NT-proBNP**	• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. • Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs futher investigation.	• Accuracy, reproducibility. • Wide availability. • High-sensitivity.	• Insufficient evidence to establish the significance of subtle rises. • Variations with different assays. • Role for routine surveillance not clearly established.

Coronary Artery Disease

- Assessment of CAD considering CT as a risk factor and based on age, gender and history
- Clinic evaluation and diagnostic tests for ischemia detection indicated to diagnose pre-existing CAD and guide the choice of CT drugs
- CT with pyrimidine analogues requires close monitoring for ischemia with regular ECGs – STOP CT if ischemia occurs
- Drug re-challenge may be considered if no alternatives (eventually pre-treatment with TNG and/or Channel blockers
- Long term F-U and ischemia tests useful for detection of CAD after CT and mainly RT

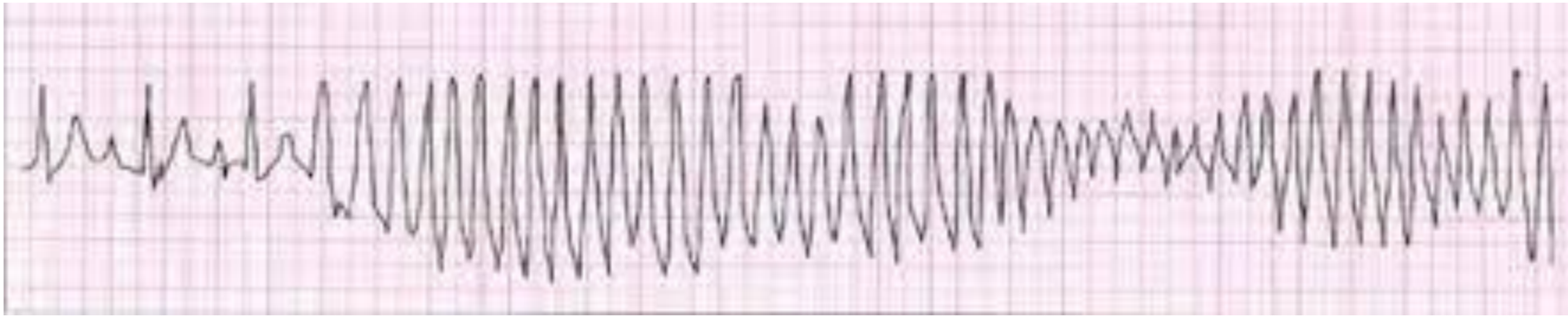
Valvular Heart Disease

- CT agents do not directly affect cardiac valves.
- VHD for pre-existing valve lesions, infective endocarditis and LV dysfunction.
- RT-induced VHD in 10% of treated patients: fibrosis and calcification of the aortic root and cusps, mitral valve annulus and base and mid portions of the leaflets.
- Mediastinal RT with 20-30 Gy, 30-year risk increased by 1.4%.
- Echocardiography assessment method of choice, at baseline and at follow-up.
- CMR and CT may be used. CT useful for calcifications of the ascending aorta.
- Cardiac surgery challenging because of mediastinal fibrosis, associated CAD, myocardial and pericardial disease and impaired wound healing. TAVI of choice.

Arrhythmias

- Basal 12 leads ECG and QTc in all patients at baseline
- Repeated periodical ECGs in patients with history of LQT, organic heart disease, other QT prolonging drugs, bradycardia, thyroid dysfunction and electrolytes abnormalities
- Discontinue treatment /alternative treatment if QTc > 500 msec or increase > 60 msec or arrhythmias development
- Careful assessment and avoid conditions favoring torsades de pointes, mainly hypokalaemia and extreme bradycardia
- Minimize exposition to other QTc prolonging drugs during CT with potentially chemotherapy at risk

- see



http://www.crediblemeds.org.

Arrhythmias

Table 10 Risk factors for QT prolongation in cancer patients

Risk factors for QT prolongation	
Correctable	**Non-correctable**
Electrolyte imbalance • Nausea and emesis • Diarrhoea • Treatment with loop diuretics • Hypokalaemia (≤3.5 mEq/L) • Hypomagnesaemia (≤1.6 mg/dL) • Hypocalcaemia (≤8.5 mg/dL) **Hypothyroidism** **Concurrent use of QT-prolonging drugs** • Antiarrhythmic • Anti-infective • Antibiotic • Antifungal • Psychotropic • Antidepressant • Antipsychotic • Antiemetic • Antihistamine	• Family history of sudden death (occult congenital LQTS or genetic polymorphisms) • Personal history of syncope • Baseline QTc interval prolongation • Female gender • Advanced age • Heart disease • Myocardial infarction • Impaired renal function • Impaired hepatic drug metabolism

Arterial Hypertension

- Monitor blood pressure before and during CT
- Management of Hypertension according to current GLs
- Early and aggressive antihypertensive treatment to prevent CV complications
- Prefer ACE-Is /ARBs, beta-blockers, dihydropyridine calcium channel blockers – Avoid due to possible drug interactions non-dihydropyridine channel blockers
- Reinforce hypotensive therapy and reduce or discontinue VEGF inhibitors if BP not controlled.
- Restart VEGF if BP controlled.

Thromboembolic Disease

Table 11 Clinical factors associated with increased risk of cancer-associated venous thromboembolism (modified from Khorana et al.[182])

Cancer-related factors • Primary site of cancer (mostly pancreas, brain, stomach, kidney, lung, lymphoma, myeloma) • Histology (specially adenocarcinoma) • Advanced stage (metastatic) • Initial period after cancer diagnosis
Patient-related factors • Demographics: older age, female sex, African ethnicity • Comorbidities (infection, chronic kidney disease, pulmonary disease, atherothrombotic disease, obesity) • History of venous thromboembolism, inherited thrombophilia • Low performance status
Treatment-related factors • Major surgery • Hospitalization • Chemotherapy and anti-angiogenic agents • Hormonal therapy • Transfusions • Central venous catheters

Peripheral Vascular Disease and Stroke

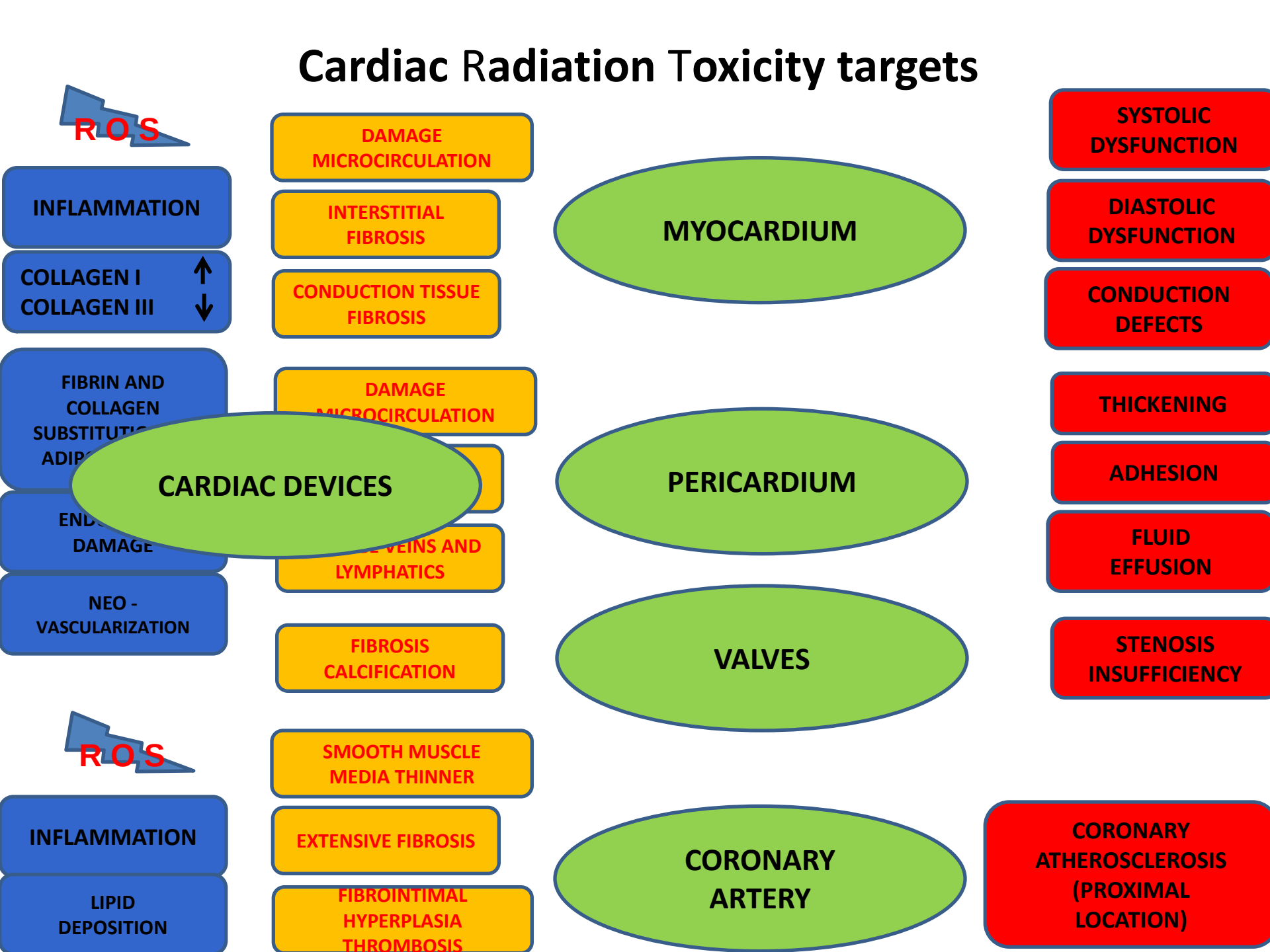
- Up to 30% of treated with nilotinib, ponatinib, and other TKI develop from first months to many years severe lower limb PAD.
- Antiplatelet drugs and, if severe PAD, revascularization
- Raynaud phenomenon
- Risk for ischaemic stroke doubled after mediastinic, cervical or cranial RT.
- Cerebrovascular ultrasound screening 5 years after irradiation and at least every 5 years.
- Aorta, other sovra-aortic vessels and iliac arteries involved

Other Conditions

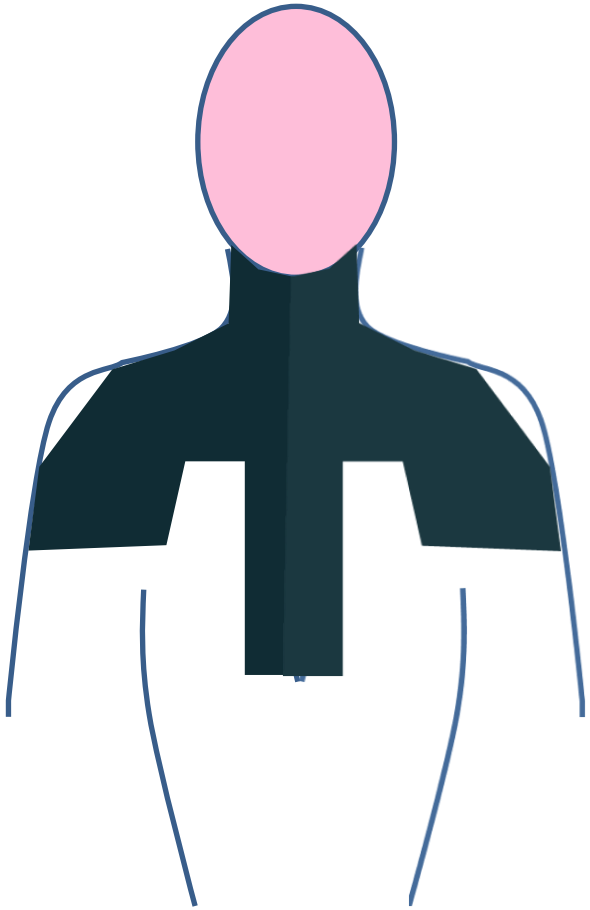
- Pericardial disease
- Pleural effusion
- Autonomic dysfunction
- Pulmonary hypertension

- Pediatric cancer population
- Elderly cancer population
- Pregnant Women

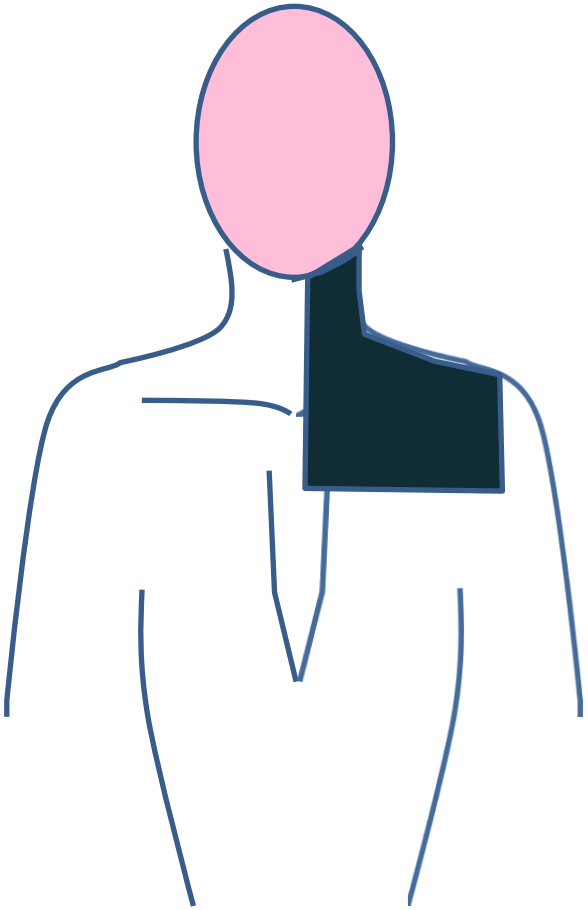
Cardiac Radiation Toxicity targets



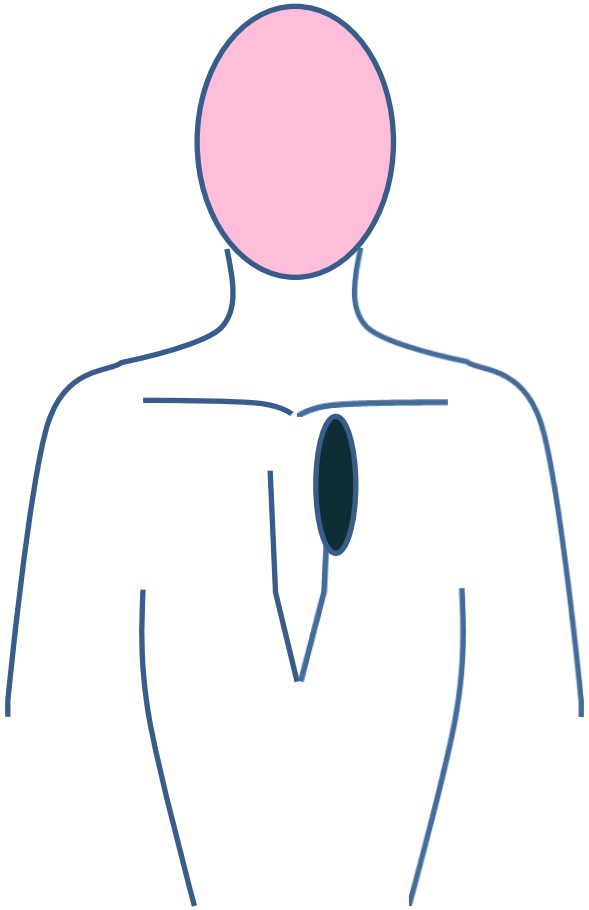
Shifting paradigm of Radiotherapy



REGIONAL RT
(ie, MANTLE RADIATION)

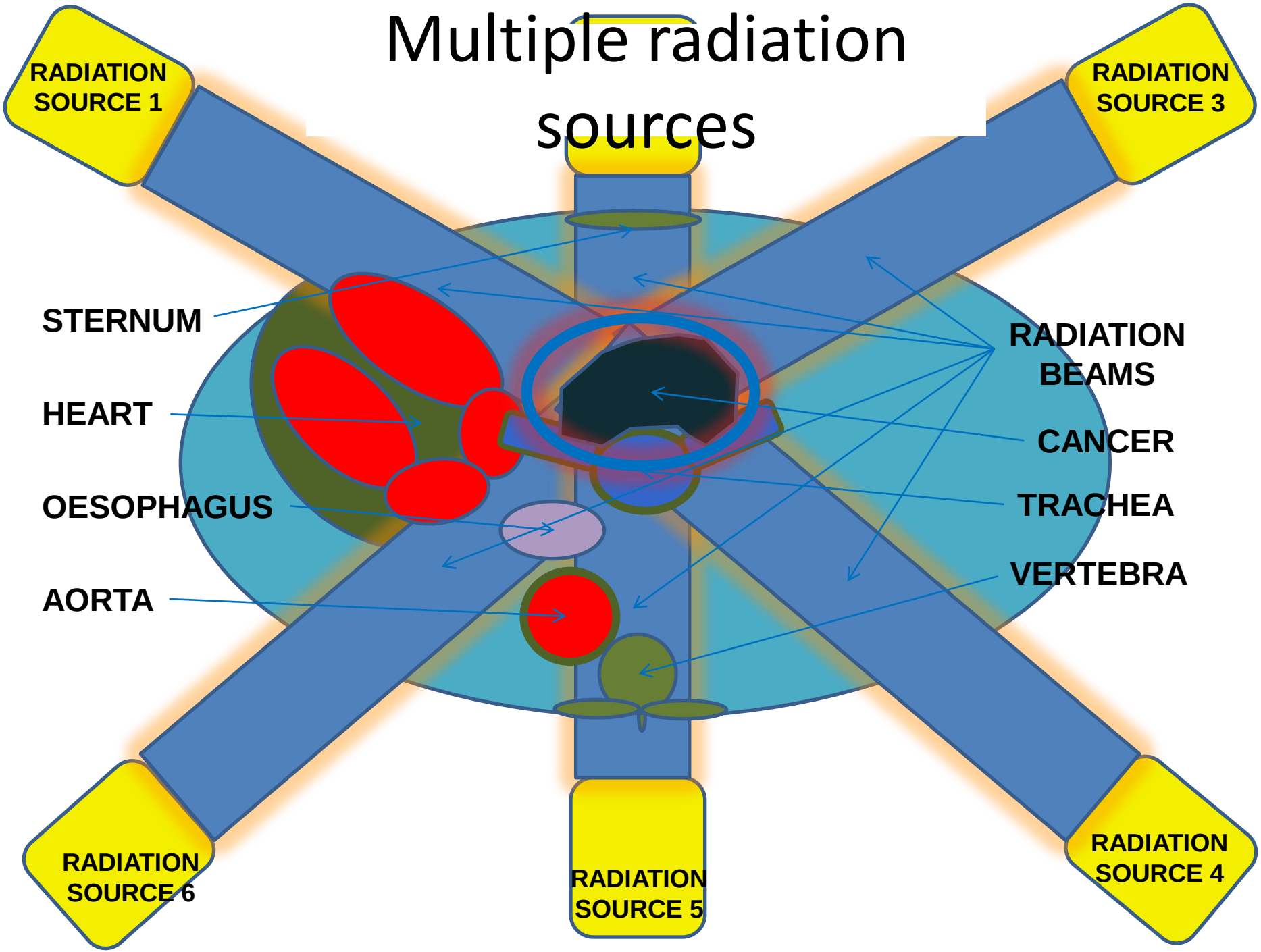


INVOLVED-FIELD RT

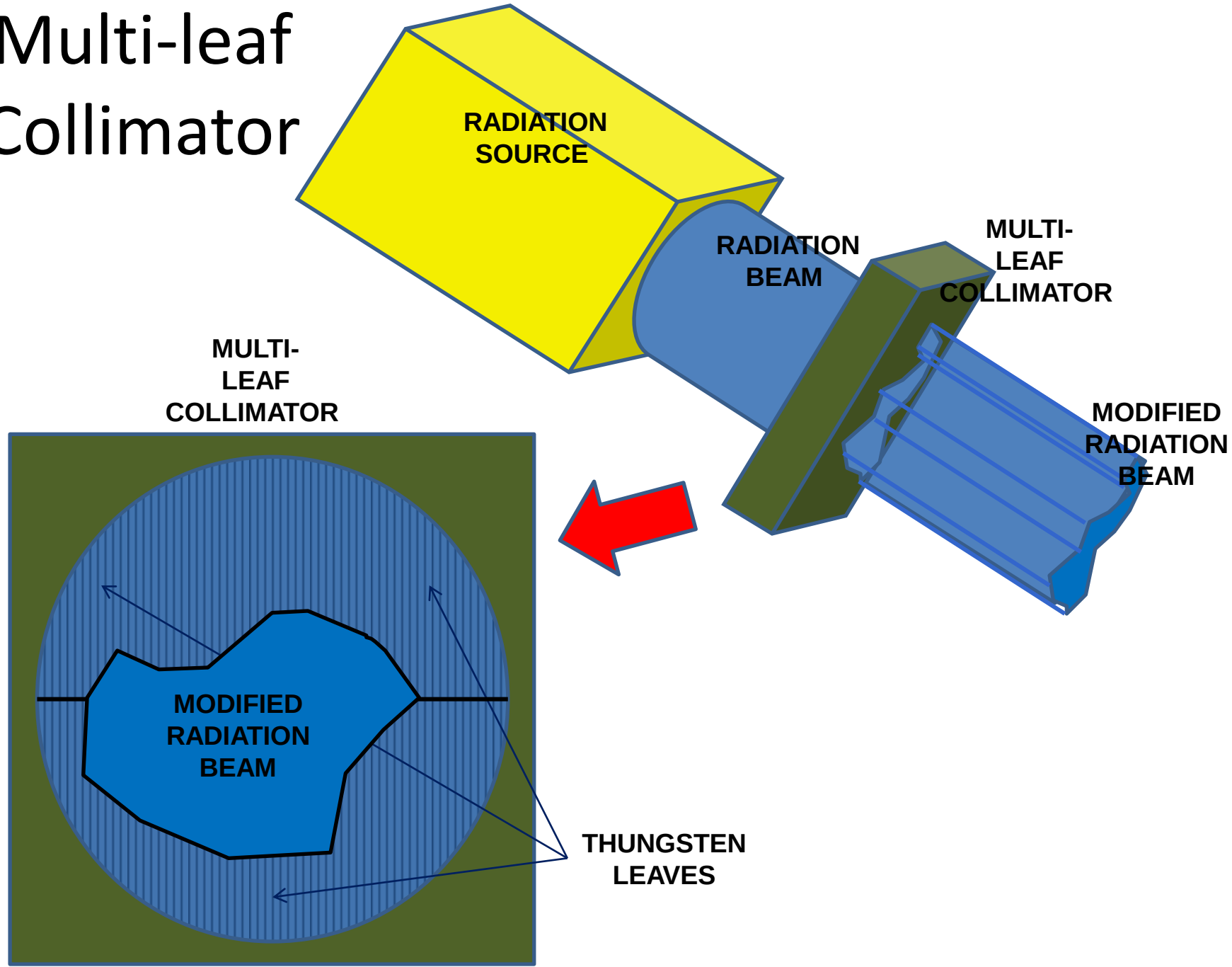


INVOLVED-NODE RT

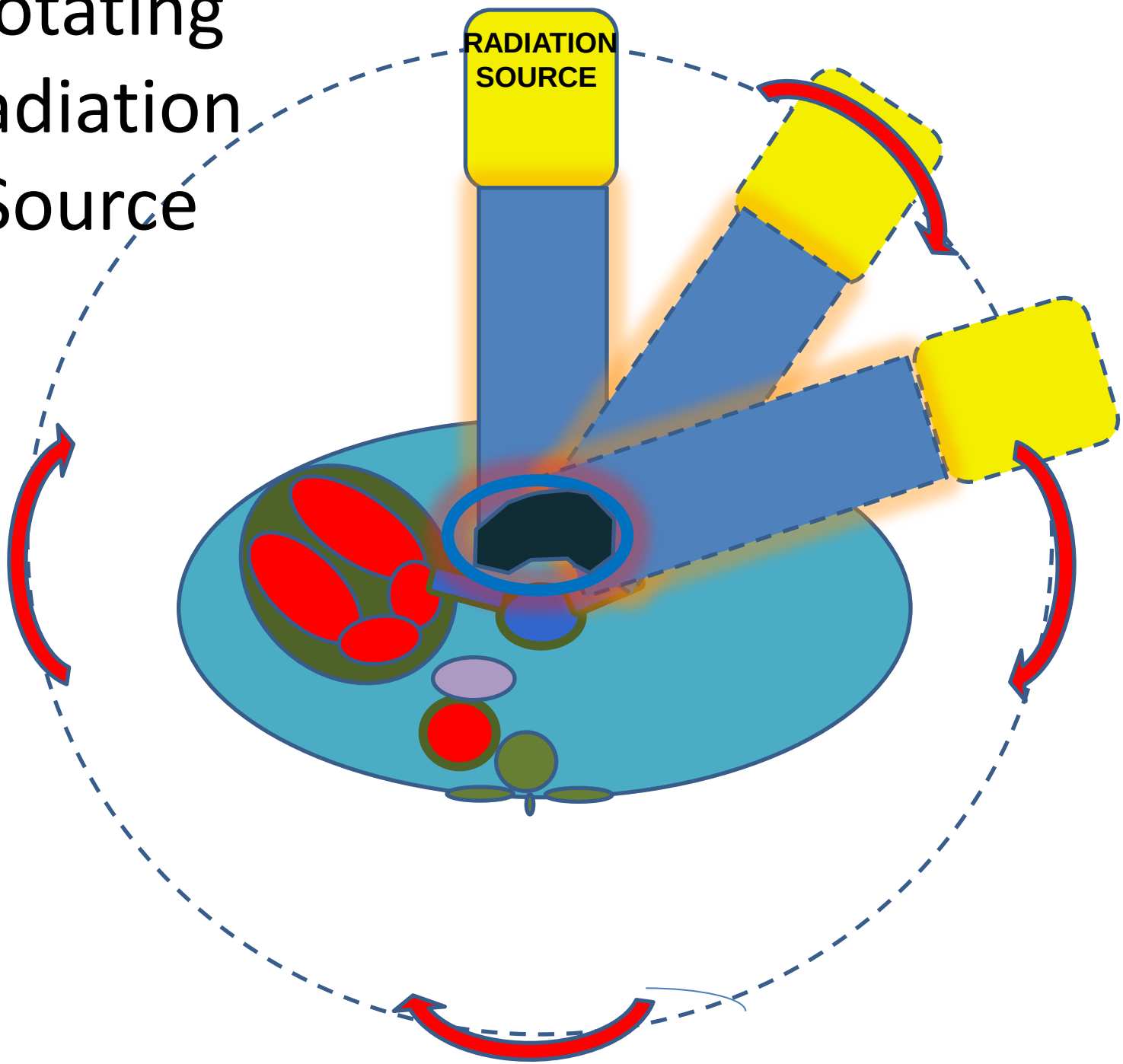
Multiple radiation sources



Multi-leaf Collimator



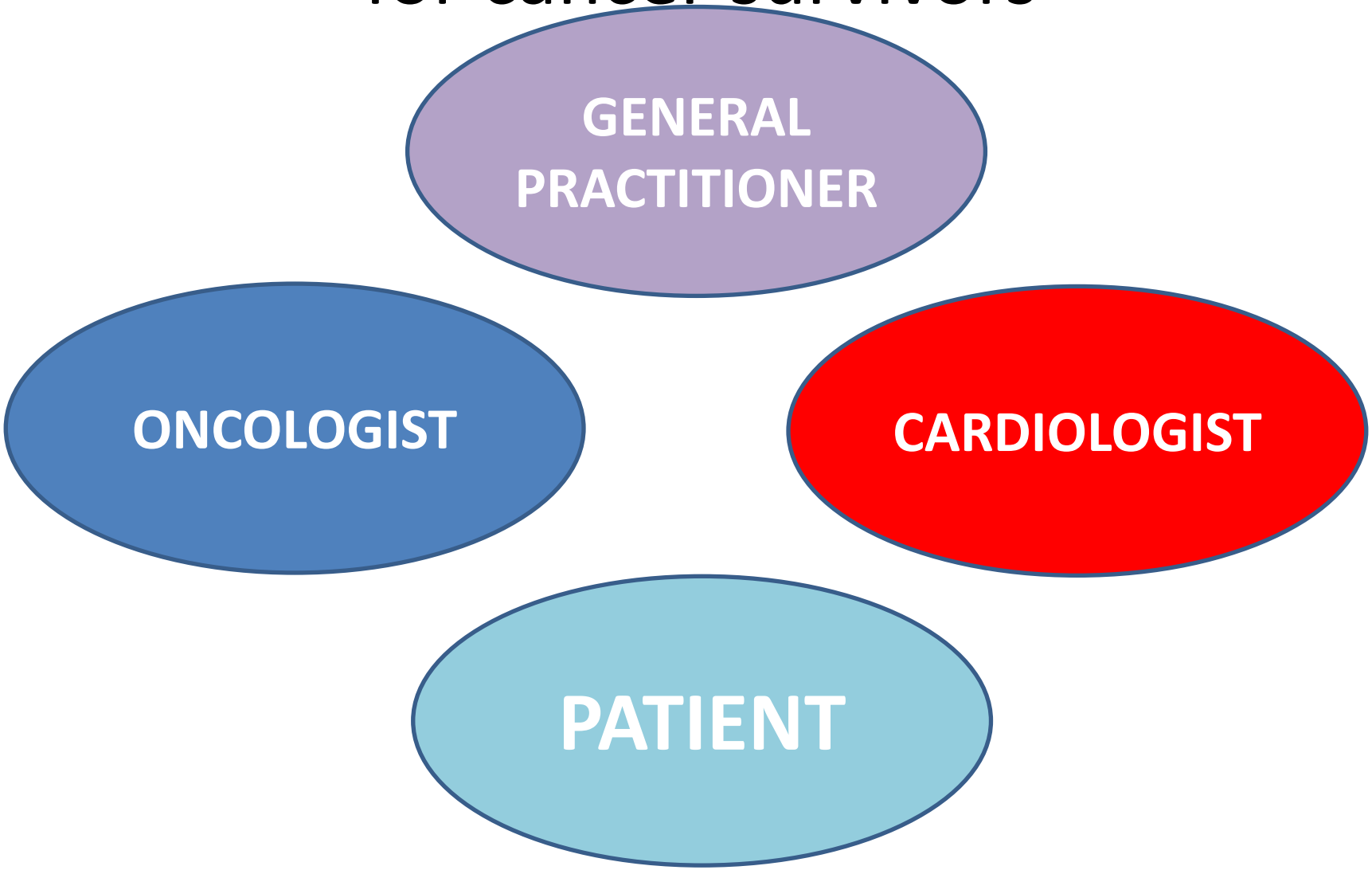
Rotating Radiation Source



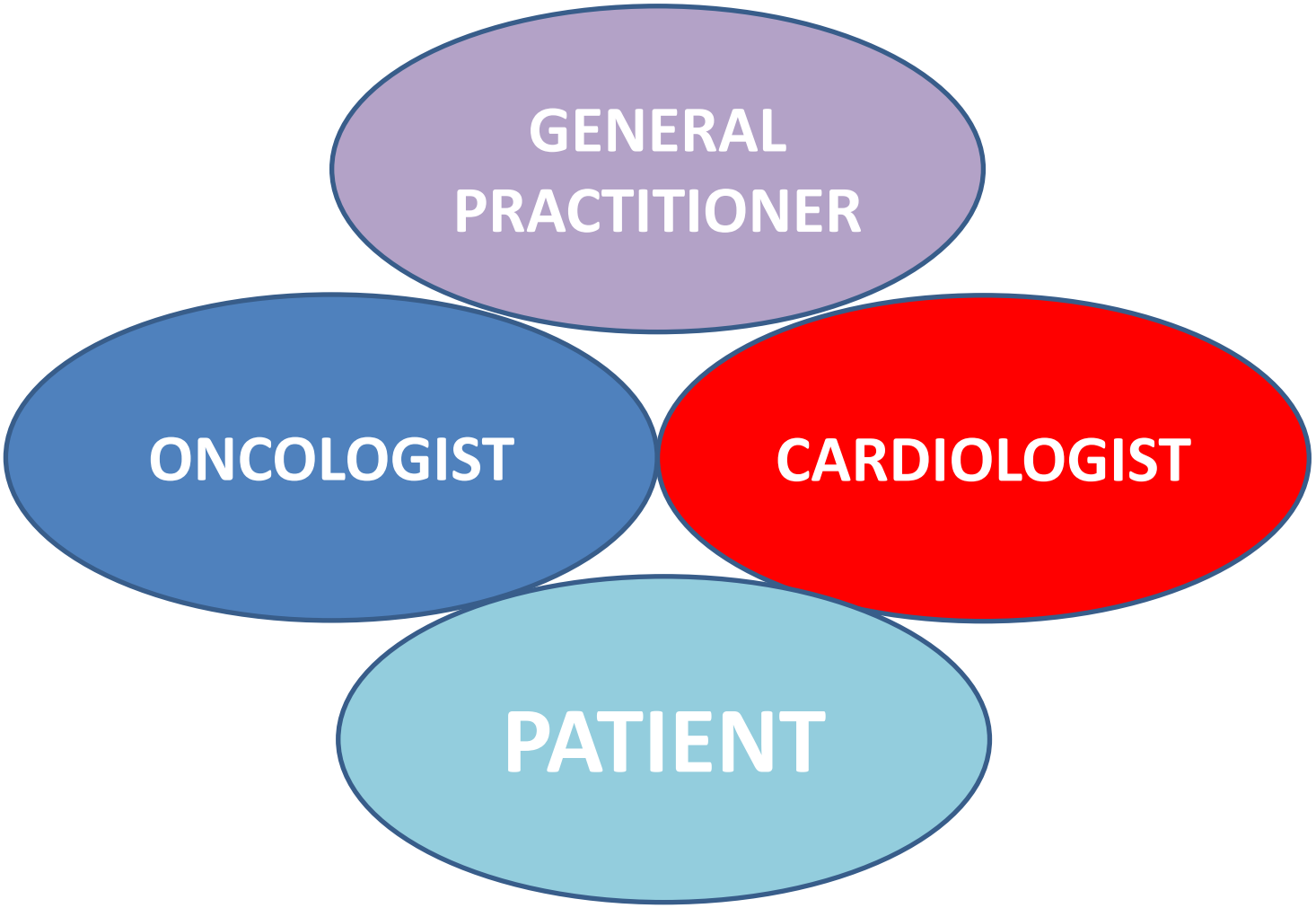
Long-term Surveillance Programs for cancer survivors

- Myocardial dysfunction
- Coronary disease
- Vascular disease
- Valvular disease

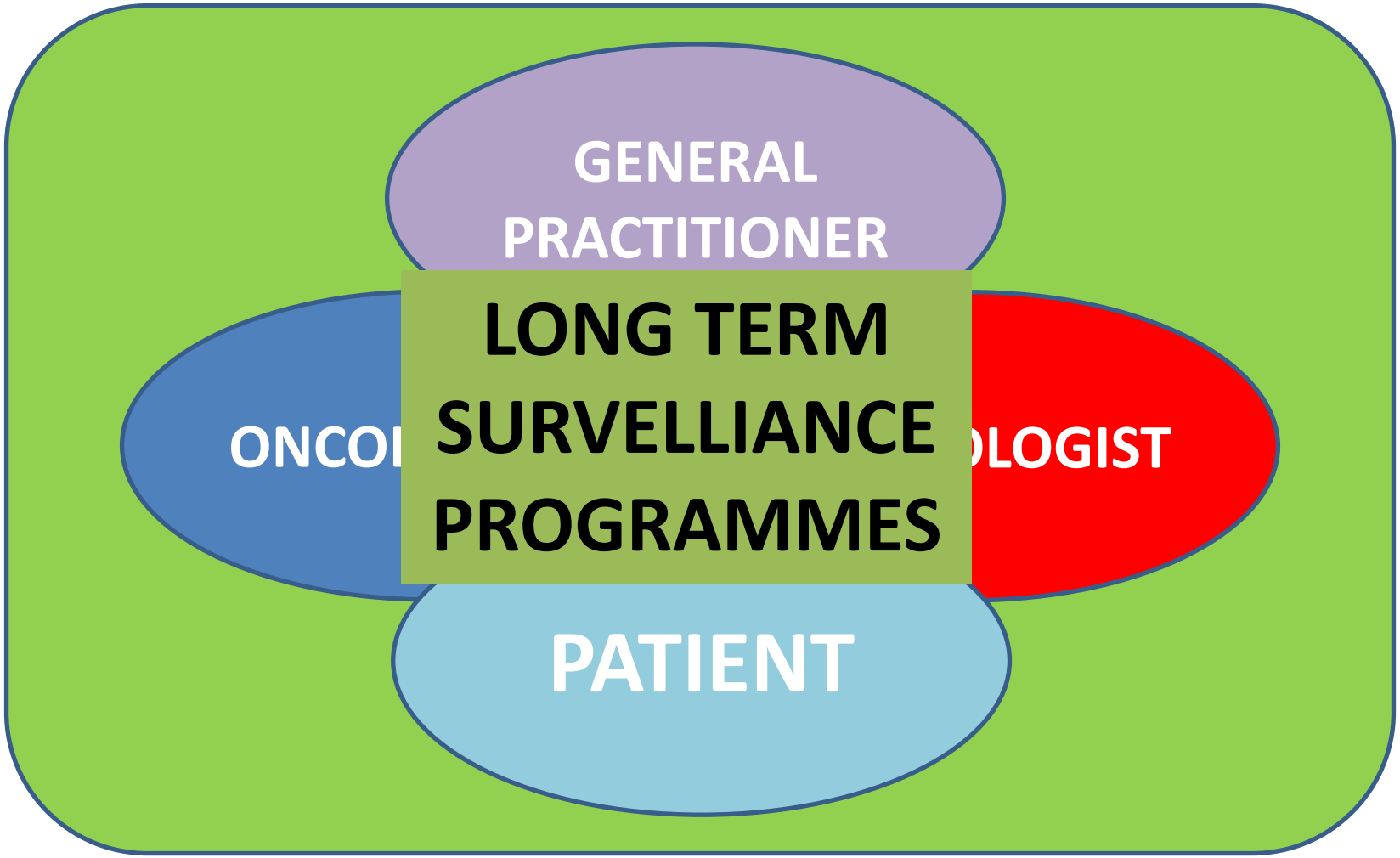
Long-term Surveillance Programmes for cancer survivors



Long-term Surveillance Programmes for cancer survivors



Long-term Surveillance Programmes for cancer survivors



Long-term Surveillance Programs for cancer survivors – Critical points

- Very few organized Cardio-Oncology Services
  - In Italy is starting a poll to know how many really they are: Candiolo (TO) IRCCS, Milan IEO, Napoli IRCCS Fondazione G. Pascale, Padua IOV, Bari IRCCS G.Paolo II, Aviano (PN) CRO
  - In Spain University Hospitals La Paz in Madrid and Bellvitge in Barcelona with C-O structures
  - In Portugal University Hospital Santa Maria, Lisbon C-O with specialized cardiologist - 3 oncology hospitals with general cardiologists.
  - In France C-O service in Marseille, Hopital Bichat Paris, Hospital St Joseph et St Luc Lyon active collaboration with Oncology Centres
  - In Belgium, Germany, Czech Republic, Norway, Rumania, Switzerland not apparently structures

Long-term Surveillance Programs for cancer survivors – Critical points

- Who is interested in Cardio-Oncology?
  - In Italy C-O WG of ANMCO – AIOM - AICO (?) -
  - In Spain C-O WG of Spanish Society of Cardiology
  - In Portugal, France, Belgium, Germany, Czech Republic, Norway, Rumania, Switzerland no apparently WGs or associations about C-O

Long-term Surveillance Programs for cancer survivors – Critical points

- Enhance Knowledge:
  - **Patients**
  - **General Practitioners**
  - **Cardiologists**
  - **Oncologists**
  - **Community**
- Communication
- Organization
- Resources
- Common Paths for Follow-Up an Management

What Essential Messages

- Reduce common CVD risk factors
- Careful elimination of risk conditions
- Does the proposed CT or RT have a cardiac toxicity?
- What kind of CVD problem may have a specific cancer treated patient?
- How frequent is a complication with a specific therapy?
- Has the patient specific risk factors for a specific therapy?
- Right balance risk/benefit of treatment (‘sliding door’) concept
- Every cancer patient may be at risk of a CVD during or after long time with CT or RT
- Long term follow-up with watch-full care