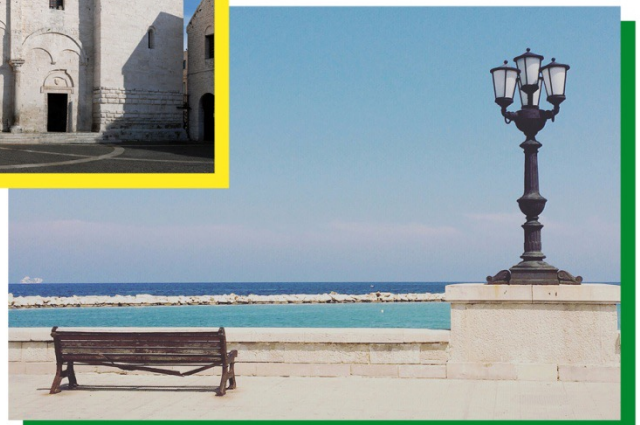
FONDAZIONE ITALIANA LINFOMI

LATE EFFECTS
GUARIRE DAL LINFOMA E VIVERE BENE



Cardiotossicità acuta e tardiva:
Prevenzione e diagnosi precoce

Agata Puzzovivo

UOSD di Cardiologia
IRCCS Giovanni Paolo II Bari
Direttore: Stefano Oliva

Bari, 17-18 febbraio 2023

Sala "A. Leogrande"
Centro Polifunzionale Studenti
Università degli Studi di Bari "Aldo Moro"

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2022 ESC Guidelines on cardio-oncology

Official ESC Guidelines slide set

- Approvate dall'Associazione Europea di Ematologia (EHA), dalla Società Europea di Radioterapia ed Oncologia (ESTRO) e dalla Società Internazionale di Cardio-Oncologia (IC-OS)

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Systematic Review

Late Cardiological Sequelae and Long-Term Monitoring in Classical Hodgkin Lymphoma and Diffuse Large B-Cell Lymphoma Survivors: A Systematic Review by the Fondazione Italiana Linfomi

Stefano Oliva [1,†], Agata Puzzovivo [1,*,†], Chiara Gerardi [2], Eleonora Allocati [2], Vitaliana De Sanctis [3], Carla Minoia [4], Tetiana Skrypets [4], Attilio Guarini [4] and Guido Gini [5]

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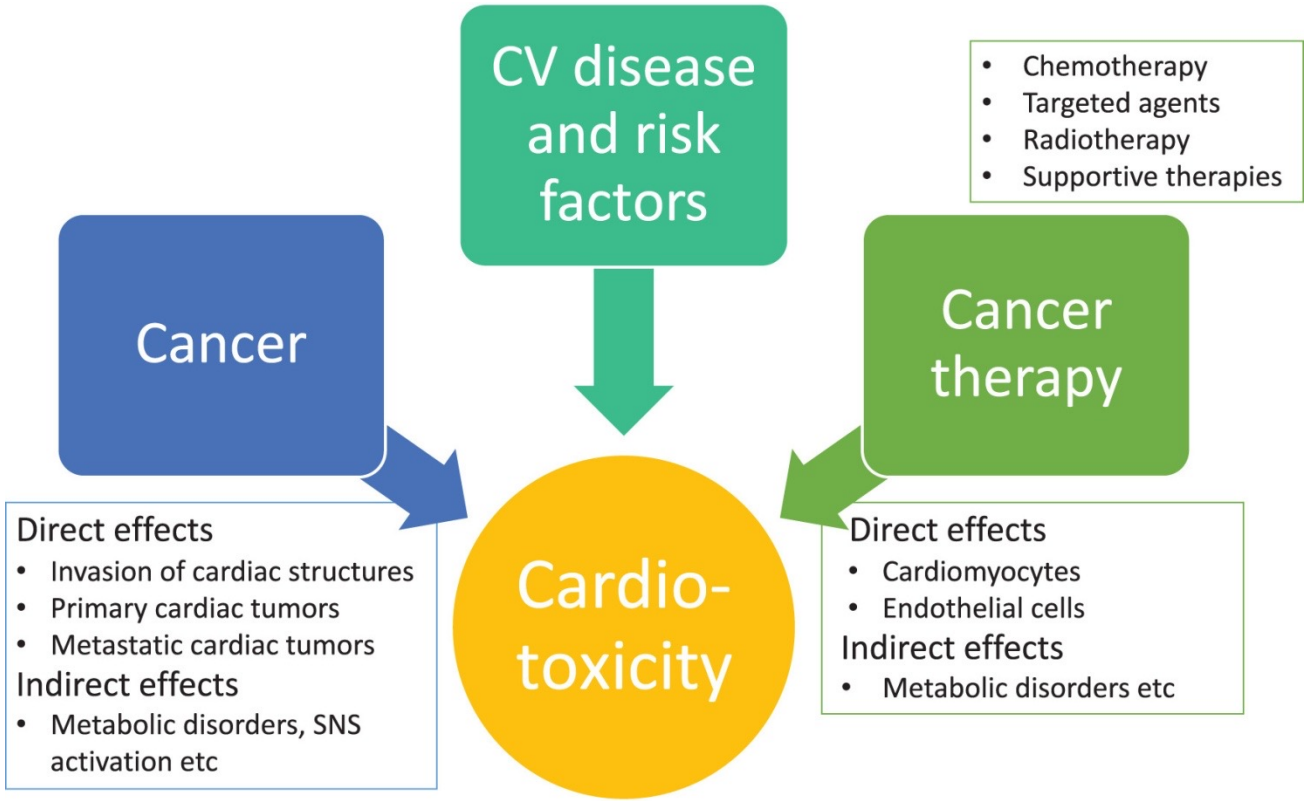
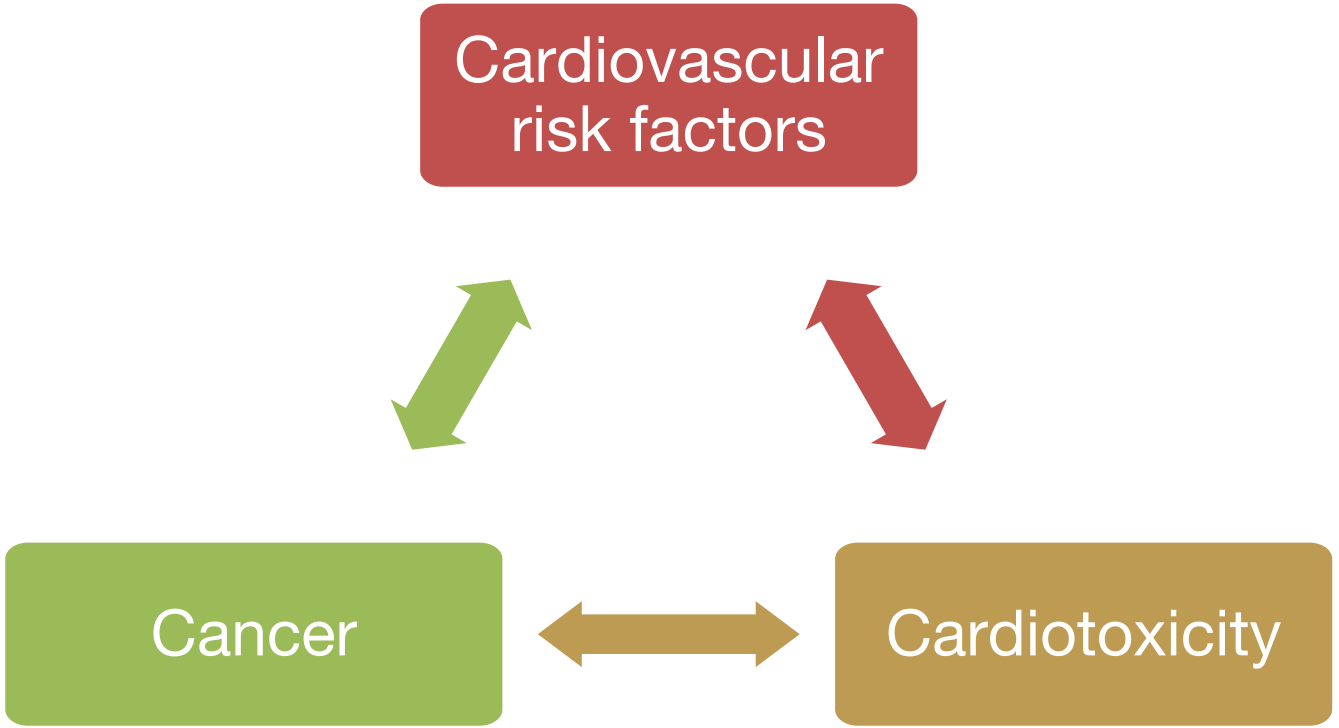
1) Incidence of cardiovascular disease (CVD)
2) Risk of long-term CVD with the use of less cardiotoxic therapies
3) Preferable Cardiovascular Monitoring for cHL and DLBCL Long-Term Survivors



Farmakis et al, European J of Heart Fail,2018


Cardiovascular risk factors
Cancer
Cardiotoxicity

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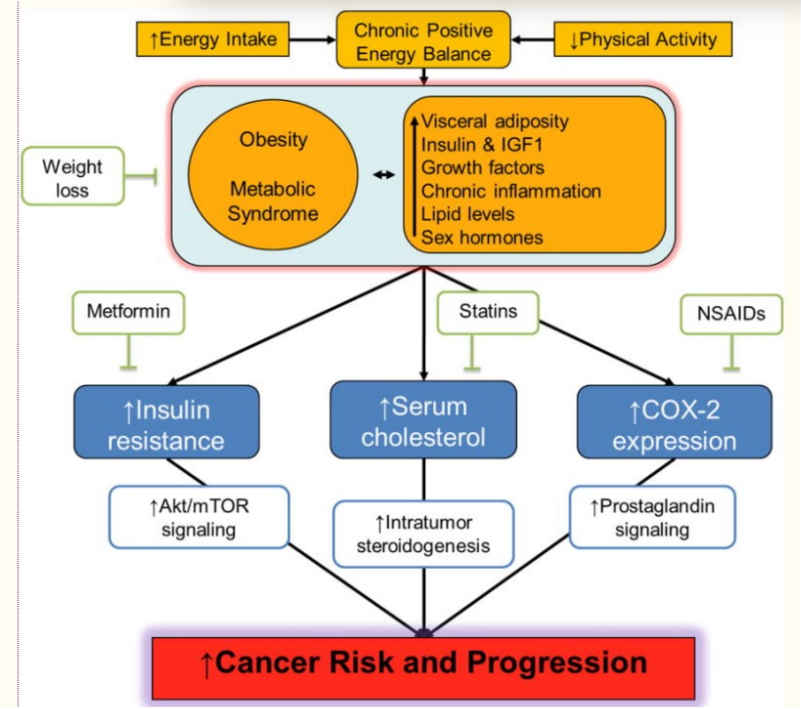
Obesity and cancer: mechanistic insights from transdisciplinary studies

Emma H. Allott[1,2] and Stephen D. Hursting[2,3]

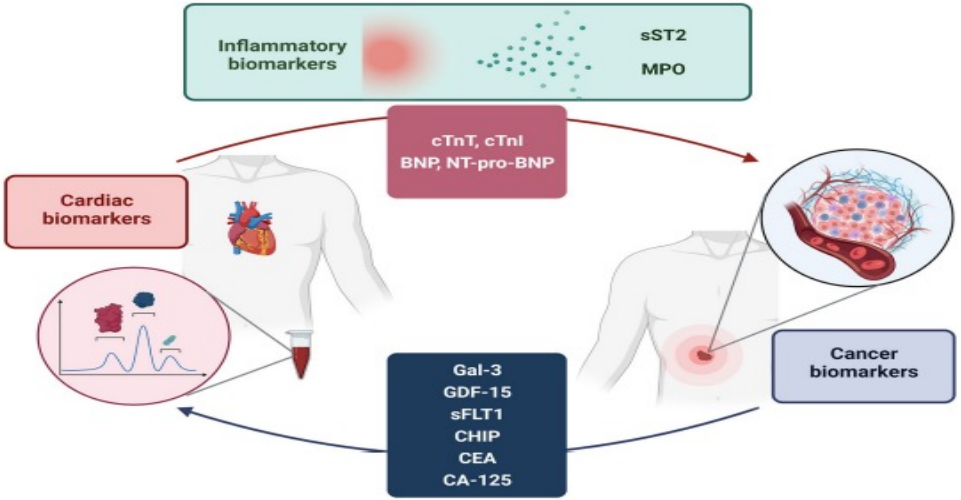


L'obesità influenza direttamente ed indirettamente il rischio oncologico e la mortalità cancro-correlata

Endocr Relat Cancer. 2015

Bidirectional Relationship Between Cancer and Heart Failure: Insights on Circulating Biomarkers

Michela Chianca[1†], Giorgia Panichella[1†], Iacopo Fabiani[2], Alberto Giannoni[1,2], Serena L'Abbate[1], Alberto Aimo[1,2], Annamaria Del Franco[1], Giuseppe Vergaro[1,2], Chrysanthos Grigoratos[2], Vincenzo Castiglione[3], Carlo Maria Cipolla[4], Antonella Fedele[4], Claudio Passino[1,2], Michele Emdin[1,2] and Daniela Maria Cardinale[4]*



Frontiers in Cardiovascular Medicine Jul 2022

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Cardiotoxicity

Spectrum of CTR-CVT presentations

CTRCD
Myocarditis
Coronary artery disease
Valvular disease
Cardiac arrhythmias
Arterial hypertension
Venous and arterial thrombosis
Peripheral vascular disease
Pulmonary hypertension
Pericardial disease

Early

-Anthracycline based chemotherapy

-Bruton's tyrosine kinase inhibitors

-Immune checkpoint inibitors

-CAR-T therapy

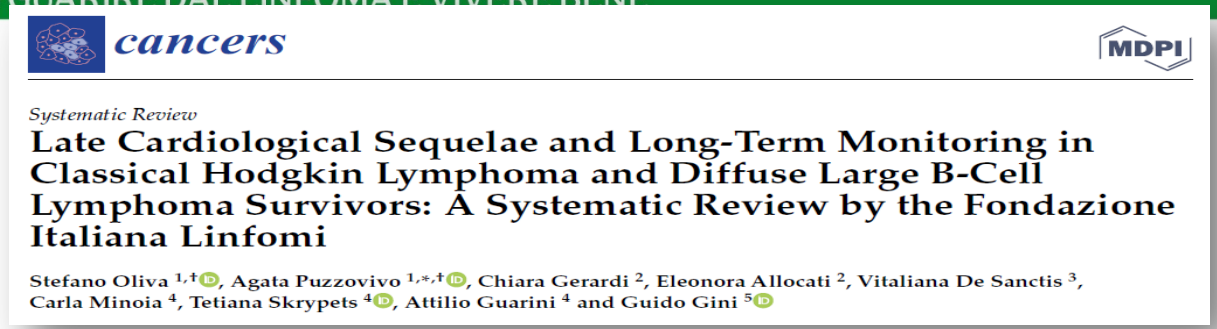
-HASCT

Late

-Anthracycline based chemotherapy

-Radiotherapy

-HASCT



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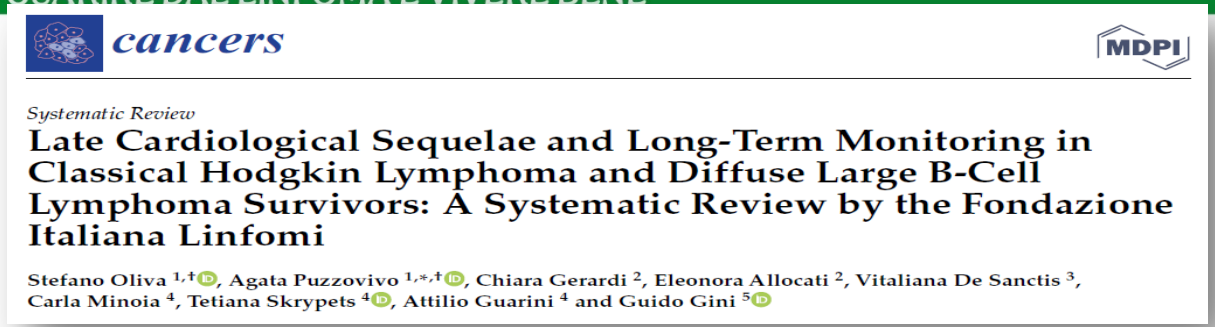
Systematic review of the literature (PubMed, EMBASE, Cochrane database) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

Incidence of CVD

- **The cumulative risk over time for CVD in this population was 3–5-fold more compared to the age-matched general population**
- **Mediastinal RT increased the risk of myocardial infarction, angina pectoris, CHF, and valvular disorders at 2–7-fold**
- **For doses above 30 Gy, a significant increase of valvular heart disease was shown over time**

Oliva S. et al, Cancers 2022



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Systematic review of the literature (PubMed, EMBASE, Cochrane database) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

Incidence of cardiovascular disease (CVD)

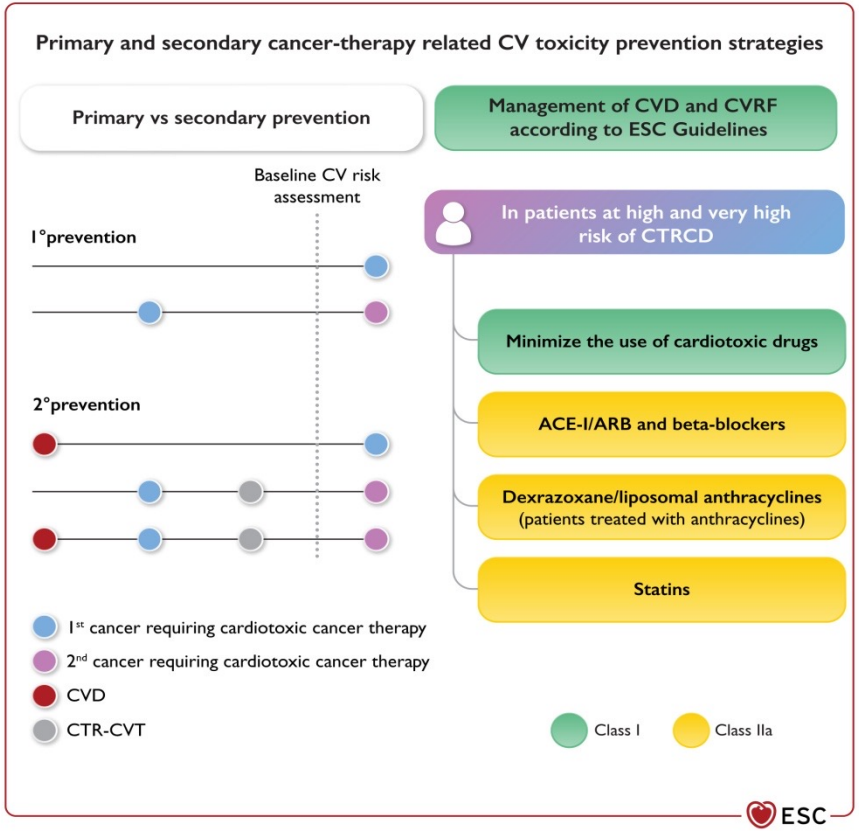
- **Compared with the sex- and age-matched general population, the risk of CHF for ASCT survivors was 4.5-fold, with an increased risk with increased age at transplant**
- **The incidence and prevalence of cardiovascular disease increased over time**
- **CHF risk increased with the number of doxorubicin prescriptions, older age, previous heart disease, hypertension, diabetes, and comorbidities**

Oliva S. et al, Cancers 2022

Primary and secondary cancer therapy-related cardiovascular toxicity prevention

Impact of prevention:

Improve outcome by
Primary prevention with
baseline CV risk assessment
Secondary in **previous CVD**
or CV toxicity



Eur Heart J, Nov 2022

Recommendations for Primary Prevention of cancer therapy-related cardiovascular toxicity (1)

Recommendations	Class	Level
Management of CVRF* according to 2021 ESC Guidelines on CVD prevention in clinical practice is recommended before, during, and after cancer therapy.	I	C
Dexrazoxane should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated.	IIa	B
Liposomal anthracyclines should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated.	IIa	B

* *Without delaying Ca treatment:*

Hypertension
Lipids, Diabetes
Smoking cessation, Alcohol moderation, Healthy life style,
Exercise beneficial during Ca therapy

Eur Heart J, Nov 2022

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Eur Heart J, Nov 2022

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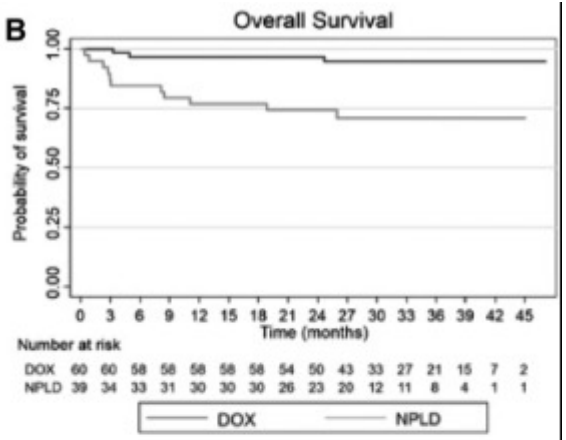
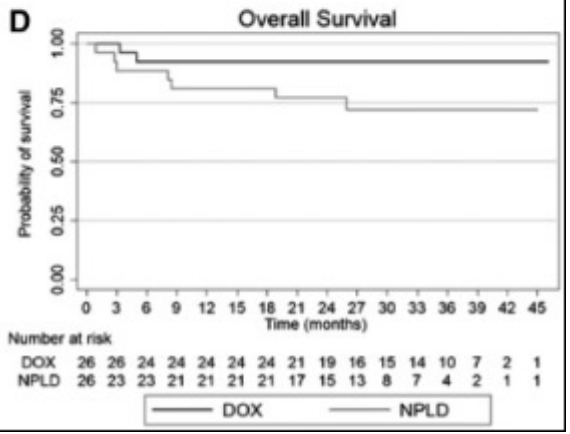
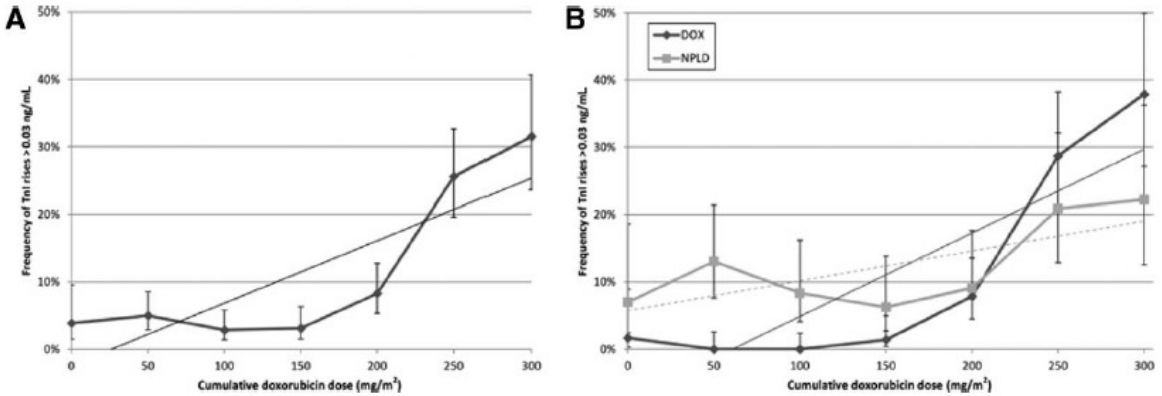




Modern Management of Anthracycline-Induced Cardiotoxicity in Lymphoma Patients: Low Occurrence of Cardiotoxicity with Comprehensive Assessment and Tailored Substitution by Nonpegylated Liposomal Doxorubicin

Jacopo Olivieri,[a,b] Gian Piero Perna,[c] Caterina Bocci,[a] Claudia Montevecchi,[a] Attilio Olivieri,[a] Pietro Leoni,[a] Guido Gini[a]
[a]Clinica di Ematologia, Università Politecnica delle Marche, Ancona, Italy; [b]UOC Medicina Interna ed Ematologia, Ospedale Generale di Zona, Civitanova Marche, Italy; [c]Cardiologia Subintensiva, Presidio "G.M. Lancisi", Azienda Ospedaliero-Universitaria "Ospedali Riuniti" di Ancona, Italy



Over treatment course, TnI rises increased linearly in the doxorubicin subgroup but modestly in the NPLD subgroup. At doxorubicin doses >200 mg/m^2 the difference was statistically significant, with more TnI rises in the doxorubicin subgroup. NPLD-treated patients did not experience higher rates of grade 3–4 adverse events.

The Oncologist 2017

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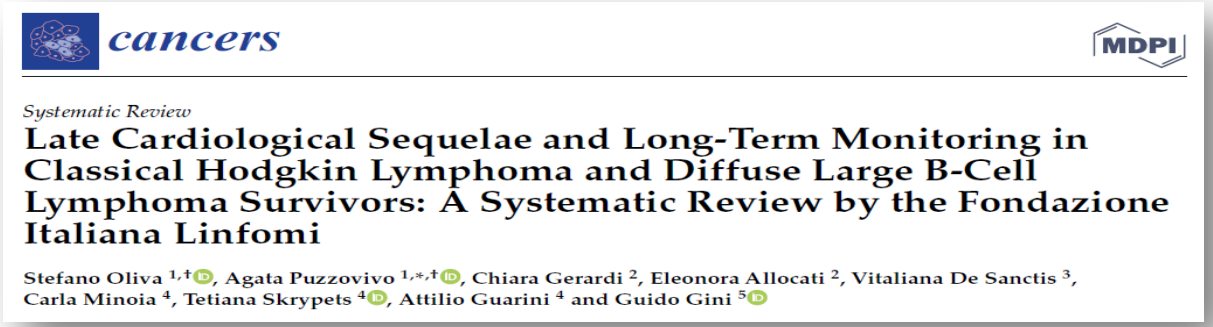
Recommendations for Primary Prevention of cancer therapy-related cardiovascular toxicity (2)

Recommendations	Class	Level
ACE-I or ARB and beta-blockers recommended for HF should be considered for **primary prevention** in high- and very high-risk patients receiving **anthracyclines** and/or **anti-HER2** therapies.	IIa	B
ACE-I or ARB and beta-blockers recommended for HF should be considered for primary prevention in high- and very high-risk patients receiving **targeted** cancer therapies that may cause HF.	IIa	C
Statins should be considered for primary prevention in adult patients with cancer at high and very high CV toxicity risk.	IIa	B

Eur Heart J, Nov 2022



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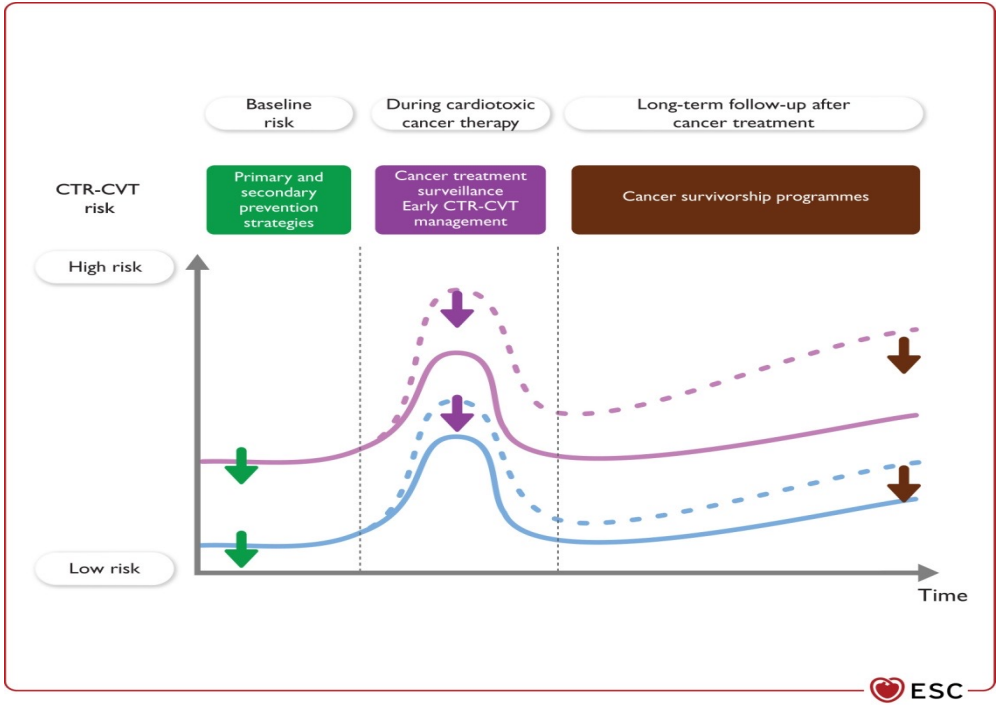
Risk of long-term CVD with the use of less cardiotoxic therapies (reduced-field radiotherapy and liposomal doxorubicin)

- **The available evidence from dosimetric studies highlights that new radiotherapy (RT) techniques reduce the risk for late cardiovascular disease (CVD)**
- **Despite the large number of reports on the use of liposomal doxorubicin in combination with cyclophosphamide, vincristine, and prednisone instead of doxorubicin in the treatment of elderly patients with DLBCL affected by cardiac disease, the authors did not find any study comparing the long-term cardiovascular risk of this regimen with the standard therapy.**

Oliva S. et al, Cancers 2022

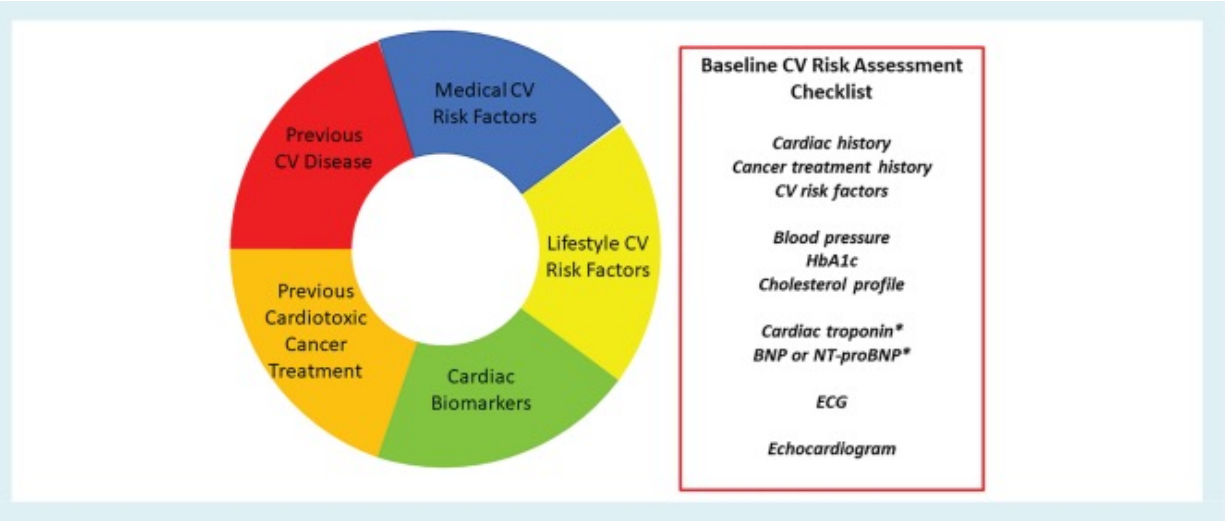
Risk assessment



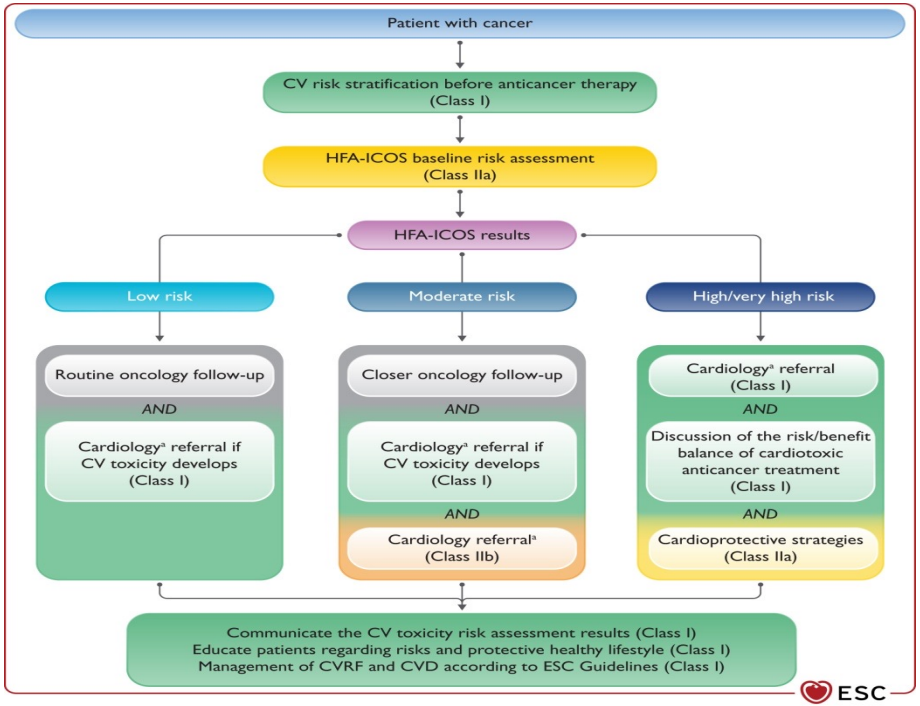
Eur Heart J, Nov 2022

ESC European Society of Cardiology
European Journal of Heart Failure (2020) 22, 1945–1960
doi:10.1002/ejhf.1920
POSITION PAPER

Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society



General cardio-oncology approach after HFA-ICOS Risk assessment



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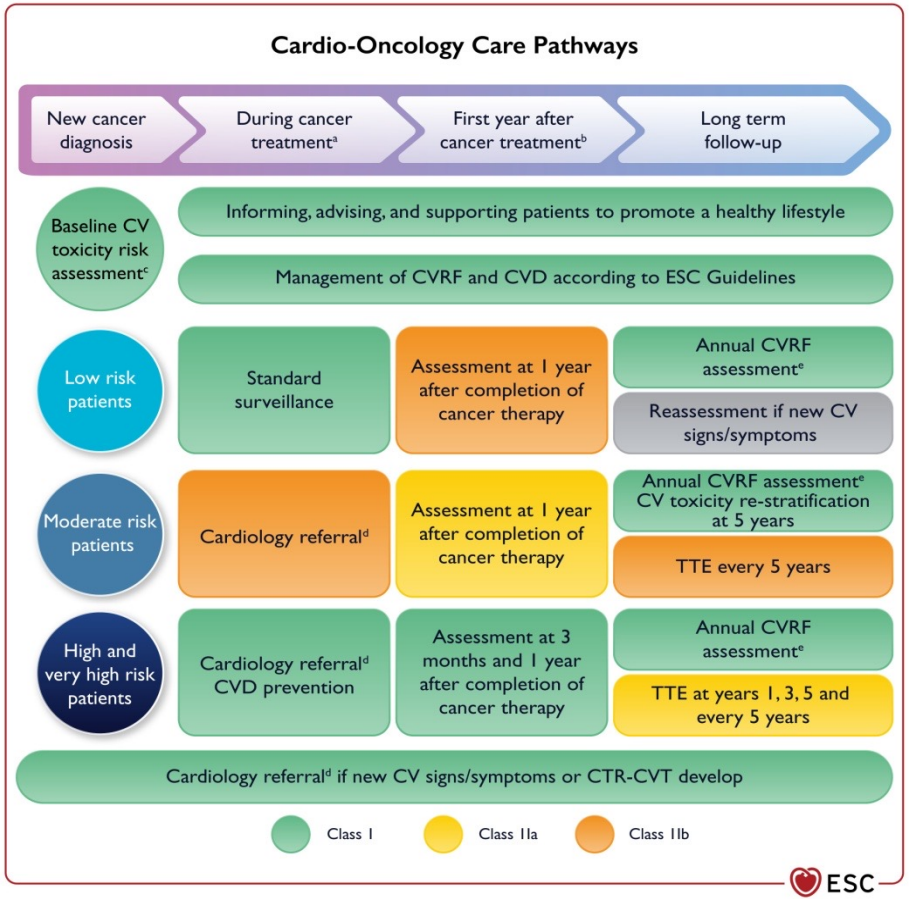

Eur Heart J, Volume 43, Issue 41, 1 Nov 2022

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Cardiovascular toxicity monitoring in patients receiving anthracycline chemotherapy

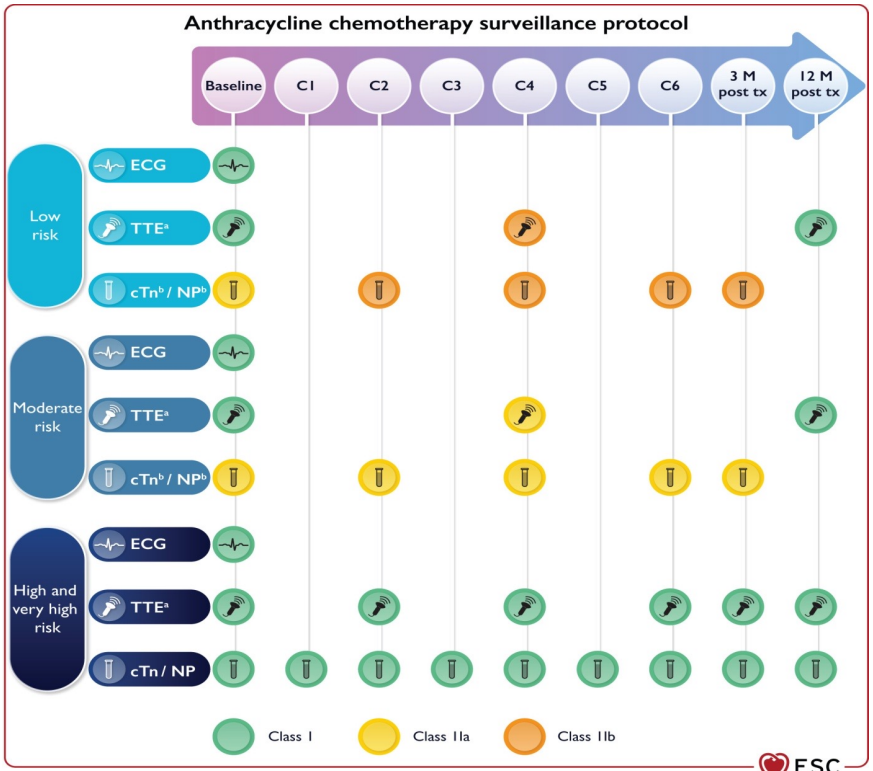
Cardiac event rates 7% - 65%

Dose dependent, cumulative.

High risk in **Doxorubicin ≥ 250** mg/m²

radiation therapy

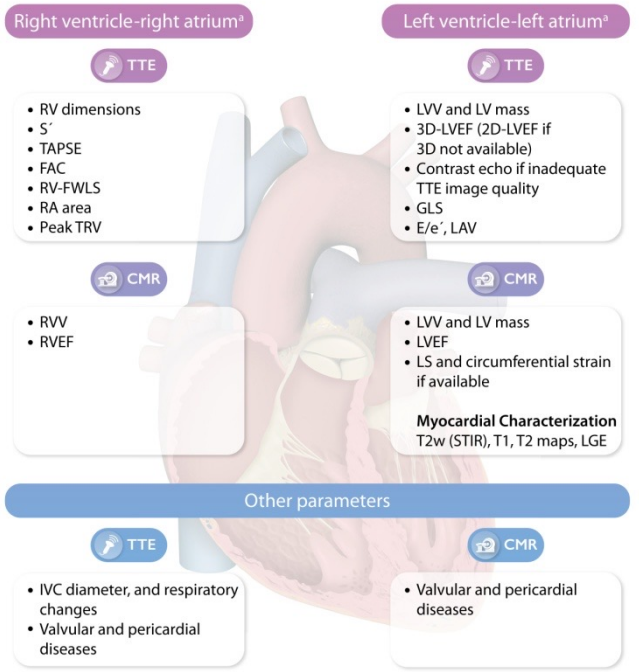
Clinical assessment combined with Trop/ NP and Echo to detect CTRCD



ESC

Eur Heart J, Nov 2022

Recommended transthoracic echocardiography and cardiac magnetic resonance imaging parameters in the evaluation of patients with cancer



Recommendations	Class	Level
General		
Echocardiography is recommended as the first-line modality for the assessment of cardiac function in patients with cancer.	I	C
3D echocardiography is recommended as the preferred echocardiographic modality to measure LVEF.	I	B
GLS is recommended in all patients with cancer having echocardiography, if available.	I	C
CMR should be considered for the assessment of cardiac function when echocardiography is unavailable or non-diagnostic.	IIa	C
MUGA may be considered when TTE is not diagnostic and CMR is not available.	IIb	C
Baseline cardiac imaging prior to potentially cardiotoxic therapies		
Baseline comprehensive TTE is recommended in all patients with cancer at high risk and very high risk of CV toxicity before starting anticancer therapy.	I	C

Eur Heart J, Nov 2022

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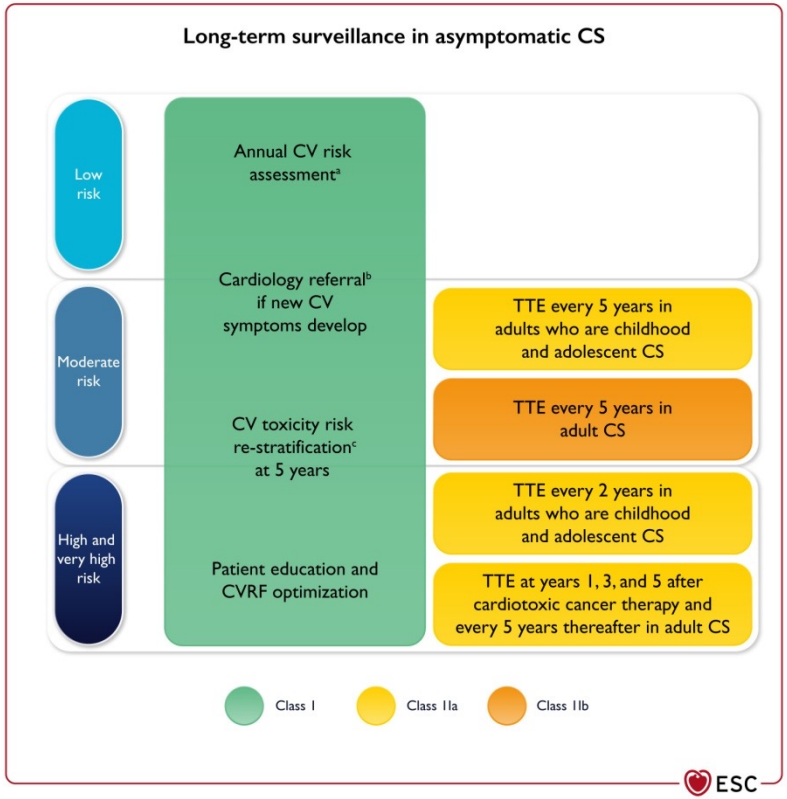
Preferable Cardiovascular Monitoring for cHL and DLBCL Long-Term Survivors

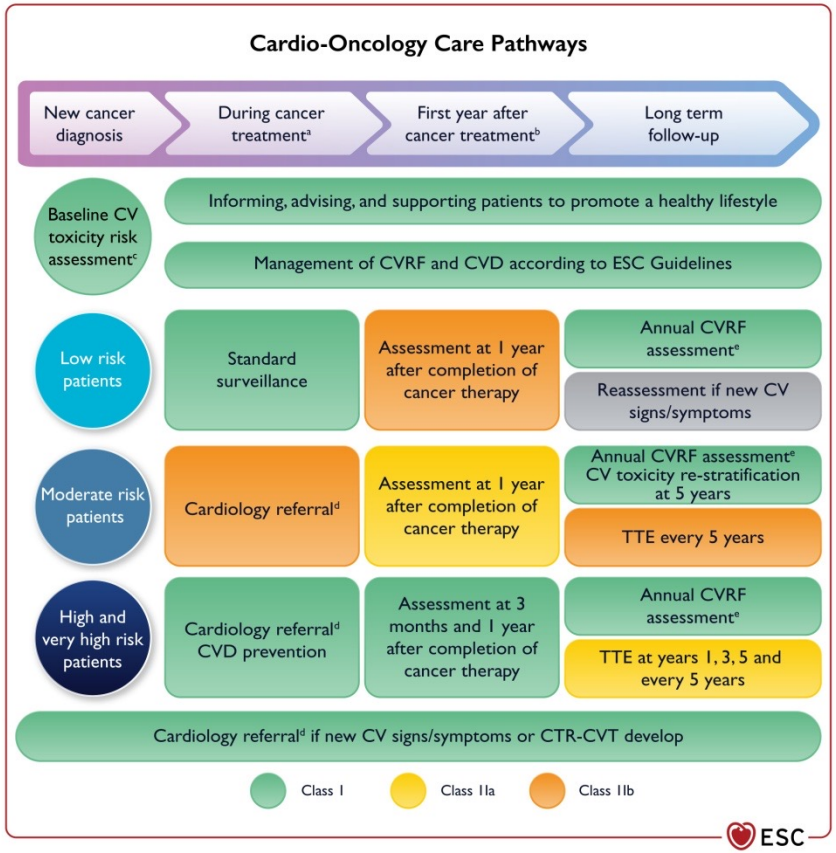
- **The routine use of cardiac MRI in follow-up is not yet feasible. However, when available, it is a very useful tool for evaluating changes in ventricular volumes and ejection fraction, particularly in patients with poor quality echocardiographic images, or if evaluation of myocardial perfusion for ischemia is also planned. Cardiac MRI is an optimal test for the global evaluation of pericardial diseases [70].**

- **FIL researchers therefore suggest a comprehensive evaluation of these parameters (LVEF, GLS, GCS, and MRI parameters)**

Oliva S. et al, Cancers 2022

Long-term follow-up in cancer survivors





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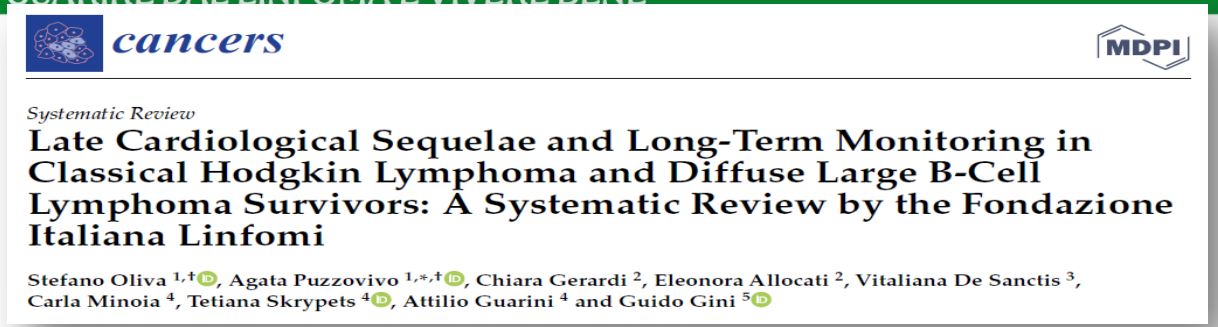

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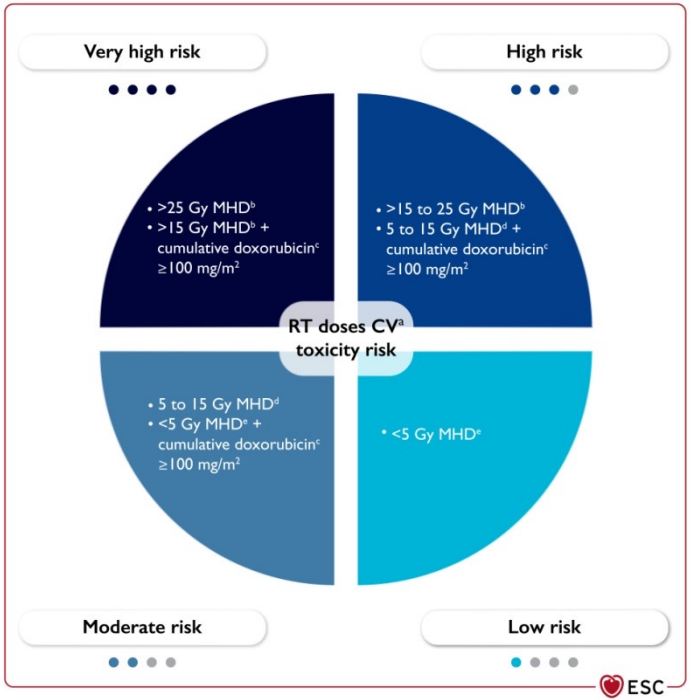
- **Although no studies are available indicating the optimal timing for early detection and monitoring of asymptomatic LV dysfunction, FIL researchers agree with the guidelines for performing an ECG plus 2D-STE echocardiographic study at 5–10 year intervals in standard-risk patients [16], while they suggest that this interval should be less than 5 years in patients at high CV risk due to the presence of the factors listed above, and then every 1–3 years. The authors also agree that a close control of CV risk factors and the promotion of healthy lifestyles should be stressed [71].**

Oliva S. et al, Cancers 2022

Radiotherapy mean heart dose and associated cardiovascular toxicity risk



Risk category	Patient characteristics
Very high risk	• Very high baseline CV toxicity risk pre-treatment • Doxorubicin ≥400 mg/m² • RT >25 Gy MHD • RT >15 to 25 Gy MHD + doxorubicin ≥100 mg/m²
Early high risk (<5 years after therapy)	• High baseline CV toxicity risk • Symptomatic or asymptomatic moderate-to-severe CTRCD during treatment • Doxorubicin 250–399 mg/m² • High-risk HSCT
Late high risk	• RT >15 to 25 Gy MHD • RT 5–15 Gy MHD + doxorubicin ≥100 mg/m² • Poorly-controlled CVRF
Moderate risk	• Moderate baseline CV toxicity risk • Doxorubicin 100–249 mg/m² • RT 5–15 Gy MHD • RT<5 Gy MHD + doxorubicin ≥100 mg/m²
Low risk	• Low baseline CV toxicity risk and normal end-of-therapy cardiac assessment • Mild CTRCD during therapy but recovered by the end of cancer therapy • RT <5 Gy MHD • Doxorubicin <100 mg/m²

Eur Heart J, Nov 2022

Recommendations for cardiovascular surveillance in asymptomatic adult cancer survivors (2)

Recommendations	Class	Level
Echocardiography may be considered every 5 years in asymptomatic moderate-risk adult CS.	IIb	C
Non-invasive screening for CAD should be considered every 5–10 years in asymptomatic patients who received >15 Gy MHD, starting at 5 years after radiation.	IIa	C
Carotid ultrasound imaging should be considered every 5 years in asymptomatic patients with a history of head/neck RT, starting at 5 years after radiation and every 5–10 years thereafter.	IIa	C
Renal artery ultrasound should be considered in patients with a history of abdominal and pelvic radiation who present with worsening renal function and/or systemic hypertension.	IIa	C

2022 ESC Guidelines on cardio-oncology
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac244)

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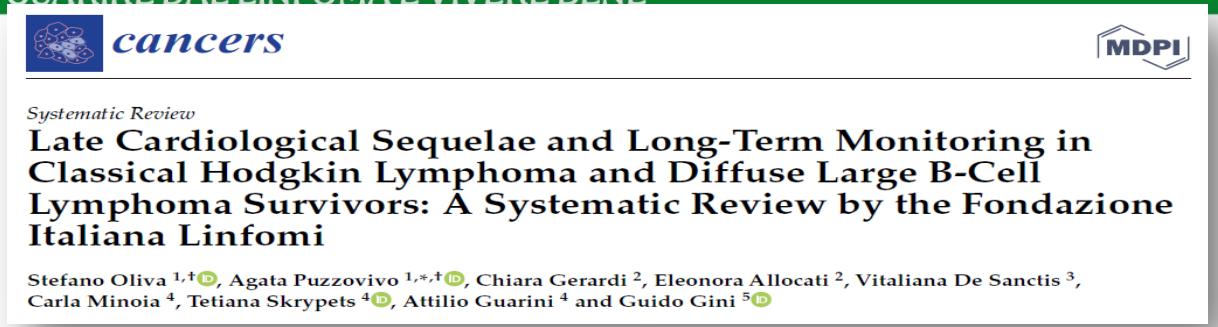
- **With regard to early detection and monitoring of CHD, FIL researchers suggest, on the basis of the available evidence, an individual risk assessment of this complication, starting from the 10th year after mediastinal radiotherapy for patients aged <45 years [50]. For asymptomatic survivors at risk for RT treatment and CV risk factors, screening with noninvasive methods such as ECG, stress-echo, or CAC measuring may be considered at intervals calculated on the basis of individual risk [73].**
- **The CAC measurement at a 5-year interval for cHL survivors with concomitant cardiovascular risk factors could be a valid option [73].**
- **A strict control of cardiovascular risk factors is always recommended.**

Oliva S. et al, Cancers 2022



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- **Many indications for the early detection and monitoring of secondary CDV derive from retrospective or uncontrolled studies; thus, data to support definitive recommendations on various tests and their frequency during follow-up of long-term lymphoma survivors still need to be implemented through ad hoc trials**

- **Further studies are also needed to detect a predictive score of cardiotoxicity, and to design a personalized surveillance that could translate into a modification of patient outcome**

Oliva S. et al, Cancers 2022

Il progetto «Cardioscore»

- Studio di registro
- 24 centri italiani partecipanti
- Oltre 1200 pazienti con DLBCL e lungo follow up
- Raccolta dati anamnestici e clinici pre-terapia e confronto con i dati in terapia e al follow up
- Analisi dei dati finalizzata alla costruzione di uno «score» di rischio predittivo rispetto alla comparsa di eventi cardiotossici nel lungo follow up
- In collaborazione con l'Istituto di Fisiologia Clinica del CNR di Pisa

Il progetto «Cardioscore»

1. **IRCCS Istituto Tumori «Giovanni Paolo II», Bari**
2. «Ospedali Riuniti», Ancona
3. A.O. «Careggi», Firenze
4. Università «La Sapienza», Roma
5. Ospedale «Businco», Cagliari
6. IRCCS «Istituto Nazionale Tumori», Milano
7. AOU Maggiore «della Carità», Novara
8. IRCCS AUSL, Reggio Emilia
9. OC, Bergamo
10. Università, Torino
11. Policlinico «San Matteo», Pavia
12. IRCCS, Candiolo (TO)
13. OC, Modena
14. Ospedale «le Molinette», Torino
15. OC, Reggio Calabria
16. AO «SS. Antonio e Biagio e Cesare Arrigo», Alessandria
17. «Spedali Civili», Brescia
18. Ospedali Riuniti «Villa Sofia-Cervello», Palermo
19. IRCCS Humanitas, Rozzano (MI)
20. Ospedale «dell'Angelo), Mestre (VE)
21. Ospedale Metropolitano «Niguarda», Milano
22. Fondazione «Policlinico Campus Biomedico», Roma
23. Ospedale «S. Maria della Misericordia», Perugia
24. CRO, Aviano (PN)

Il Progetto «Cardioscore»

Stefano Oliva, Guido Gini

FINALITA' del Cardioscore:

1. «Quantificare» il rischio in maniera oggettiva e non soggettiva;
2. Scegliere in maniera più consapevole lo schema terapeutico (rapporto costo/beneficio);
3. Definire di timing di controlli al follow up in maniera coerente con il profilo di rischio cardioncologico
4. Ottimizzare le risorse economiche e definire percorsi clinico-diagnostici personalizzati

FONDAZIONE ITALIANA LINFOMI

Grazie

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