

PLACE



PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

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GESTIONE CARDIOLOGICA NEL PAZIENTE ANZIANO CHE RICEVE TRATTAMENTI ONCOLOGICI: UN PROBLEMA NON DA POCO

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Cardio-Oncology in the Older Adult

Reddy P, Shenoy C and Anne H. Blaes AH,

- Age-related risk factors and a high prevalence of comorbidities are reasons for increased cardiotoxicity in older adults.
- Concerns regarding cardiotoxicity may lead to undertreatment, resulting in suboptimal outcomes.
- A multi-disciplinary approach based on close collaboration between oncologists and cardiologists is essential
- There is an urgent need for geriatric-specific evidence to help tailor care for this vulnerable group.

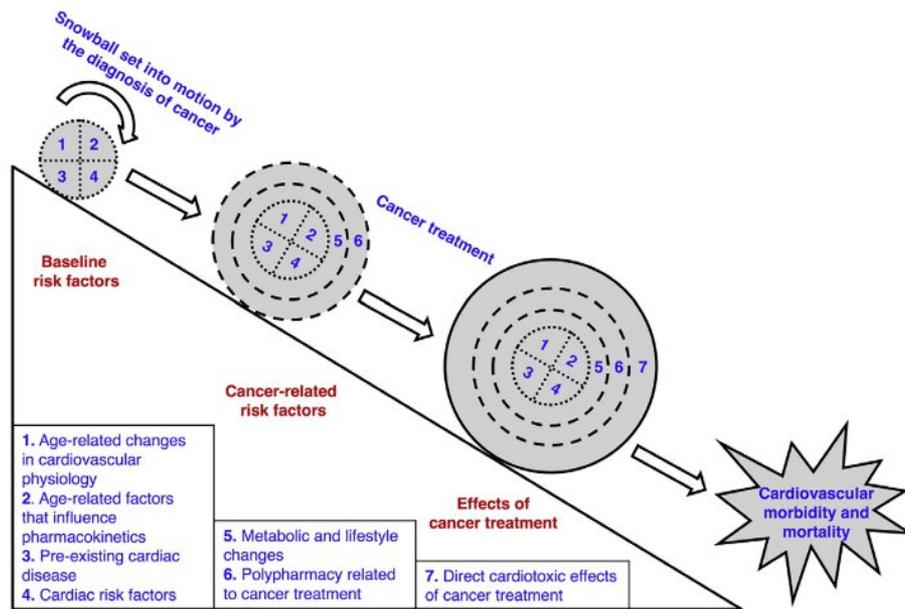


Fig. 1. The "snowball effect" resulting in cardiovascular complications of cancer therapy in older adults. See text for details. Adapted with permission from Shenoy et al. [13].

Anzianità e fragilità

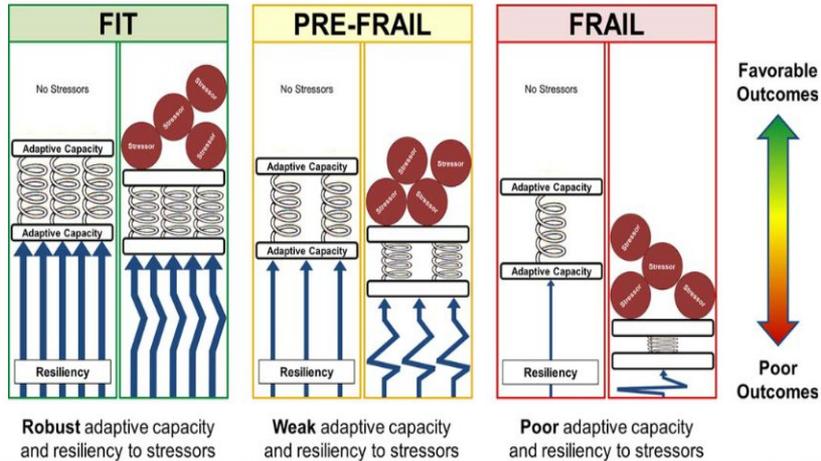


FIGURE 1. A Model for Defining Frailty. Fit patients have robust adaptive capacity and resiliency to stressors, which leads to more favorable outcomes. Prefrail patients have weakened adaptive capacity and resiliency to stressors, and frail patients have poor adaptive capacity and resiliency to stressors. Prefrail and frail patients are at greater risk of poor outcomes following surgery, chemotherapy, and radiotherapy. Figure adapted from: Robinson TN, Walston JD, Brummel NE, et al. Frailty for surgeons: review of a National Institute on Aging conference on frailty for specialists. *J Am Coll Surg.* 2015;221:1083-1092.¹³

Ethun, C.G., Bilen, M.A., Jani, A.B., Maithel, S.K., Ogan, K. and Master, V.A. (2017), Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology. *CA: A Cancer Journal for Clinicians*, 67: 362-377. <https://doi.org/10.3322/caac.21406>

The prevalence and outcomes of frailty in older cancer patients: a systematic review

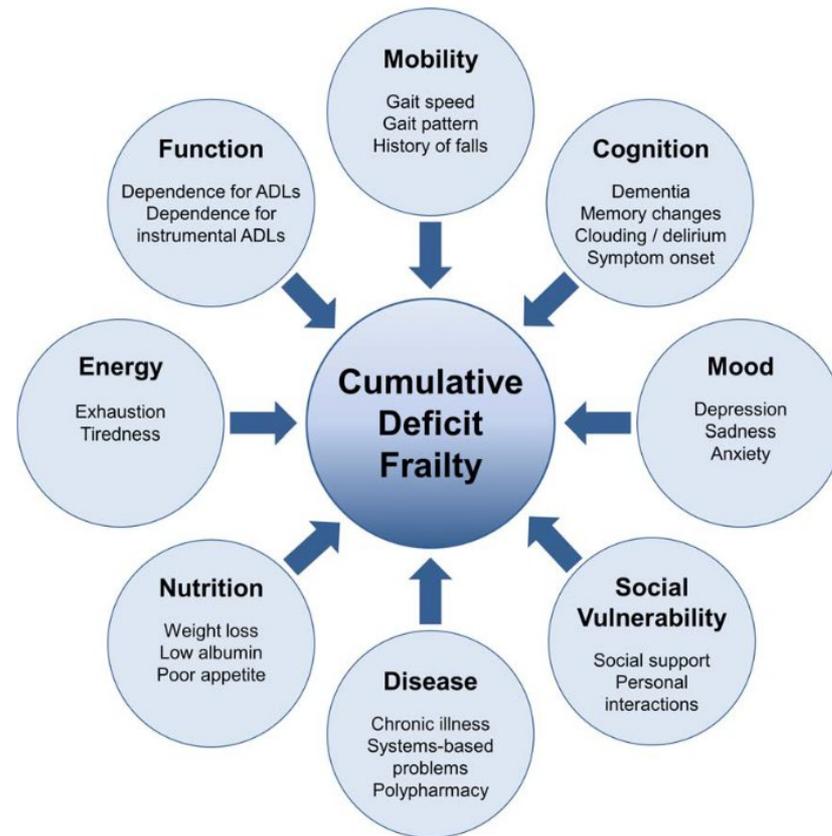
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- >40% di frail in pazienti oncologici anziani
- >40% pre-frail
- Associato a mortalità, complicanze postop, intolleranza a CT



- Comorbidità
- Perdita di peso involontaria
- Velocità del cammino
- Decadimento cognitivo
- Depressione
- Disabilità
- Sensazione di fatigue, malessere
- Handgrip (<30 Kg)
- 5 chair rise (15 sec)
- Parametri biologici (Hb, Albumina)
- Polifarmacoterapia



Comorbidity index: 10/17
patologie sono
cardiovascolari o
oncologiche

Charlson ME et al. (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases* 40, 373–383

Quan H et al. (2011) Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *American Journal of Epidemiology* 173, 676–682.

Table 1. Classical and updated Charlson comorbidity index weights

Comorbid conditions ^{a,b}	cCCI weights	uCCI weights
Myocardial infarction	1	0
Congestive heart failure	1	2
Peripheral vascular disease	1	0
Cerebrovascular disease	1	0
Dementia	1	2
Chronic pulmonary disease	1	1
Rheumatic disease	1	1
Peptic ulcer disease	1	0
Mild liver disease	1	2
Diabetes without chronic complication	1	0
Diabetes with chronic complication	2	1
Hemiplegia or paraplegia	2	2
Renal disease	2	1
Any malignancy without metastasis	2	2 ^c
Leukemia	2	
Lymphoma	2	
Moderate or severe liver disease	3	4
Metastatic solid tumour	6	6
AIDS (excluded asymptomatic infection)	6	4
Maximum comorbidity score	33	24

cCCI, classical Charlson comorbidity index; uCCI, updated Charlson comorbidity index. AIDS, acquired immunodeficiency syndrome.

^aDefinition of conditions are listed in Supplementary Table S1 (available on the Cambridge Core website).

^bTo calculate CCI the following comorbid conditions were mutually exclusive: diabetes with chronic complications and diabetes without chronic complications; mild liver disease and moderate or severe liver disease; and any malignancy and metastatic solid tumour.

^cIncluding leukemia and lymphoma.



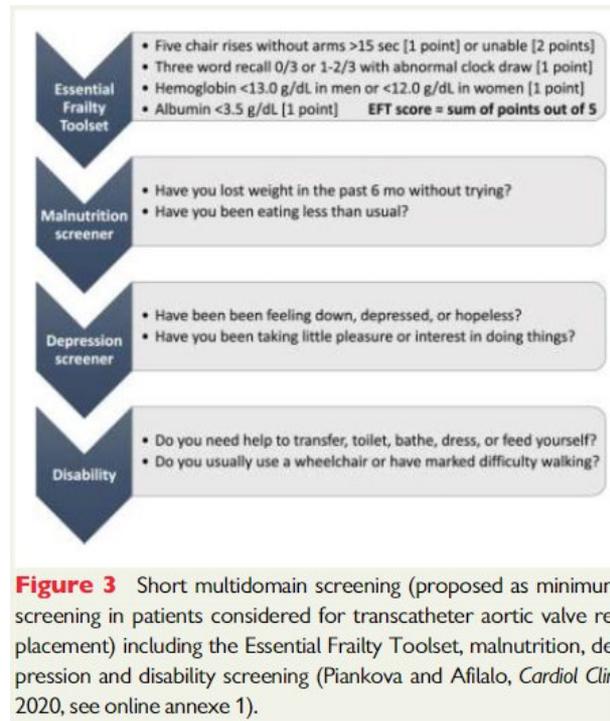


Molti score di valutazione geriatrica sono di difficile applicazione (CGA: 64 strumenti da 2 a 12 item)

Semplificazioni per scopi mirati: es TAVI

ECOG: molto usato per chemio, ma «generico»

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but <u>ambulatory</u> and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

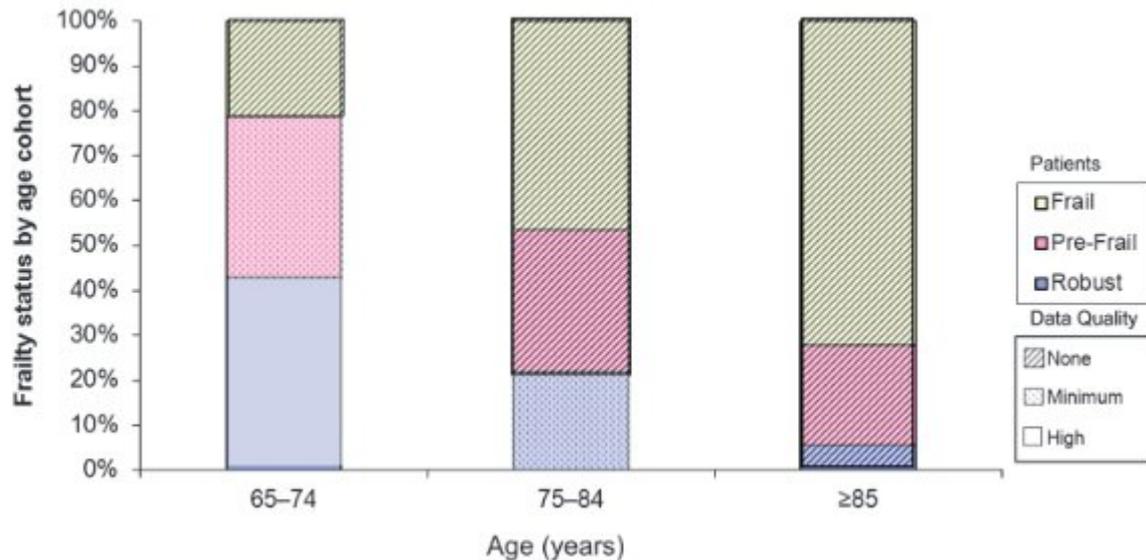




Pazienti «esclusi» dalla letteratura scientifica

Frail x Elderly

Figure 1. Percentage of robust (0 of 5 deficits), pre-frail (1–2 of 5 deficits), and frail (3 or more deficits) older adults in three age groups and the quality of the evidence regarding appropriate cancer treatments by age. Based on data from Fried et al. (54).



William Dale, et al. on behalf of the Cancer and Aging Research Group

Biological, Clinical, and Psychosocial Correlates at the Interface of Cancer and Aging Research

JNCI: Journal of the National Cancer Institute, Volume 104, Issue 8, 18 April 2012, Pages 581–589, <https://doi.org/10.1093/jnci/djs145>



UNDERREPRESENTATION OF PATIENTS 65 YEARS OF AGE OR OLDER IN CANCER-TREATMENT TRIALS

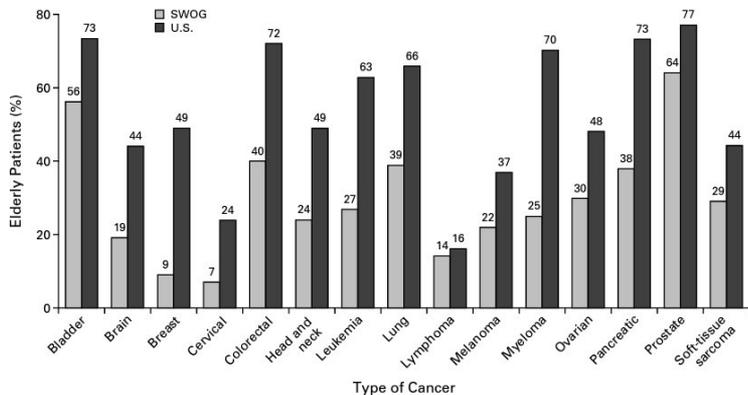


Figure 3. Proportion of Elderly Patients (65 Years of Age or Older) in Trials of the Southwest Oncology Group (SWOG) as Compared with the Proportion of Elderly Patients in the U.S. Population of Patients with Cancer, According to the Type of Cancer. The differences between the two groups were significant ($P < 0.001$) for all types of cancer except lymphoma.

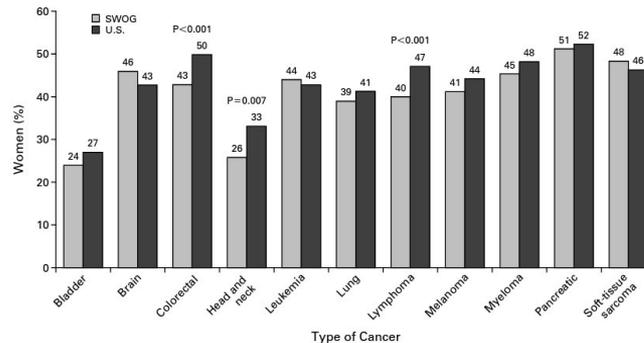
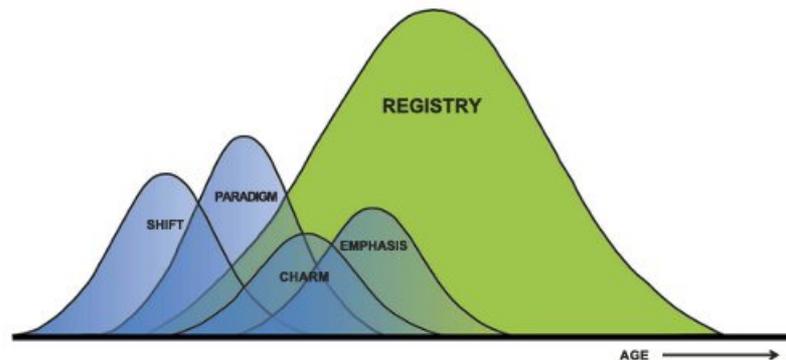


Figure 1. Proportion of Women Enrolled in Trials of the Southwest Oncology Group (SWOG) as Compared with the Proportion of Women in the U.S. Population of Patients with Cancer, According to the Type of Cancer.

Elles M. Screever, Wouter C. Meijers, Dirk J. van Veldhuisen & Rudolf A. de Boer (2017) New developments in the pharmacotherapeutic management of heart failure in elderly patients: concerns and considerations, Expert Opinion on Pharmacotherapy, 18:7, 645-655, DOI: 10.1080/14656566.2017.1316377





Trastuzumab

Il rischio di
cardiotossicità è
aumentato da età

Table 1 Summary of studies evaluating clinical risk factors for development of trastuzumab-induced cardiomyopathy [5, 15–26]

Trial	Number of patients	Population studied	Primary risk factor for TIC	Statistical significance of primary risk factor	Other risk factors for TIC	
Previous anthracycline use						
Leung et al. [15]	116,342	 Elderly patients receiving trastuzumab	Previous anthracycline use	$p < 0.00001$	 Older age, hypertension, diabetes	
Chen et al. [5]	45,537		Breast cancer patients receiving adjuvant therapy	Incidence rate ratio = 1.66		
Jawa et al. [16]	6,527		Breast cancer patients receiving trastuzumab	OR = 2.14		
Naumann et al. [17]	388		Women who received trastuzumab	Older age among those who had received prior anthracycline $p = 0.001$		
Farolfi et al. [18]	179		Breast cancer patients receiving adjuvant trastuzumab	Cumulative dose of Doxorubicin > 240 mg/m ² or Epirubicin > 500 mg/m ² OR = 3.07		No other studied risk factors were statistically significant
Cardiac risk factors						
Chavez-MacGregor et al. [19]	9,535	  Breast cancer patients over age 65 receiving chemotherapy	Coronary artery disease	HR 1.82	 Hypertension, age > 80	
Ezaz et al. [20]	1,664		Elderly women receiving adjuvant trastuzumab	Coronary artery disease		HR 2.16
Gunaldi et al. [21]	111	 HER2+ breast cancer patients who received trastuzumab	Coronary artery disease, obesity	$p < 0.0001$	 Smoking, hypertension, post-menopausal	
Guenancia et al. [22]	8,745		Breast cancer patients who received anthracycline or sequential anthracycline and trastuzumab	Obesity		OR = 1.47
Tang et al. [23]	160		Breast cancer patients receiving adjuvant trastuzumab	History of myocardial infarction		$p < 0.001$
Baron et al. [24]	76	 Inner city breast cancer patients receiving trastuzumab	African American race	$p < 0.05$	 No other studied risk factors were statistically significant	
Serrano et al. [25]	45		Breast cancer patients over age 70 receiving trastuzumab	Diabetes		$p = 0.01$
Baseline borderline ejection fraction (EF)						
Romond et al. [26]	944	Patients receiving trastuzumab	Baseline EF 50–54%	$p < 0.001$	 Age	

OR odds ratio, HR hazard ratio

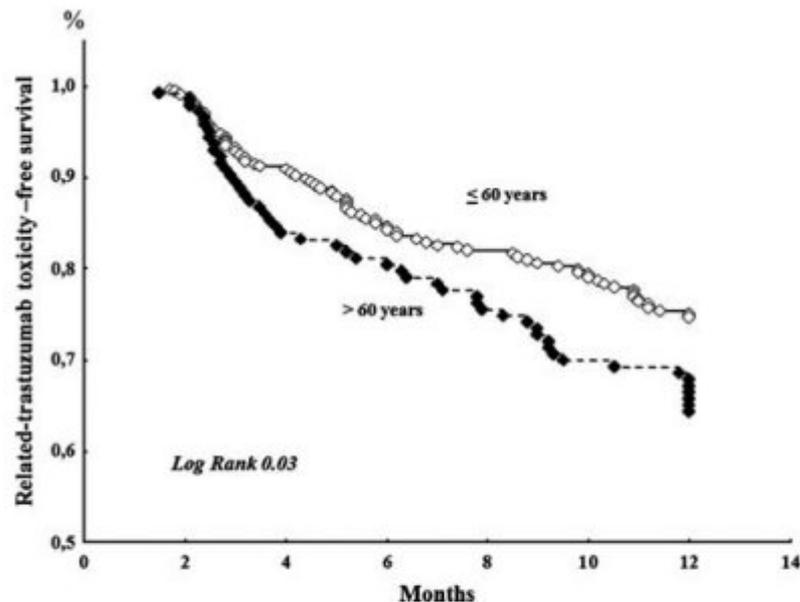


Figure 2 Related-trastuzumab cardiotoxicity-free survival (Kaplan–Meier curves) in patients older (black diamonds) and younger (white circles) than 60 years of age.

Pazienti esposti a ANT prima di trastuzumab, pre 2010

Tarantini, L., Gori, S., Faggiano, P., Pulignano, G., Simoncini, E., Tuccia, F., Ceccherini, R., Bovelli, D., Lestuzzi, C., Cioffi, G., & ICARO (Italian CARDio-Oncologic) Network (2012)

Adjuvant trastuzumab cardiotoxicity in patients over 60 years of age with early breast cancer: a multicenter cohort analysis.

Annals of oncology : official journal of the European Society for Medical Oncology, 23(12), 3058–3063.
<https://doi.org/10.1093/annonc/mds127>



HER2 target therapies

Table 3 Baseline cardiovascular risk stratification proforma for HER2-targeted cancer therapy (pertuzumab, T-DM1, lapatinib, neratinib)

Risk factor	Score	Level of evidence
Previous cardiovascular disease		
Heart failure or cardiomyopathy	Very high	C
Myocardial infarction or CABG	High	B
Stable angina	High	B
Severe valvular heart disease	High	C
Baseline LVEF <50%	High	C
Borderline LVEF 50–54%	Medium ²	B
Arrhythmia ^a	Medium ²	C
Cardiac biomarkers (where available)		
Elevated baseline troponin ^b	Medium ²	B
Elevated baseline BNP or NT-proBNP ^b	Medium ²	C
Demographic and cardiovascular risk factors		
Age ≥80 years	High	B
Age 65–79 years	Medium ²	B
Hypertension ^c	Medium ¹	B
Diabetes mellitus ^d	Medium ¹	C
Chronic kidney disease ^e	Medium ¹	C
Current cancer treatment regimen		
Includes anthracycline before HER2-targeted therapy	Medium ^{1f}	B
Previous cardiotoxic cancer treatment		
Prior trastuzumab cardiotoxicity	Very high	C
Prior (remote) anthracycline exposure ^g	Medium ²	B
Prior radiotherapy to left chest or mediastinum	Medium ²	C
Lifestyle risk factors		
Current smoker or significant smoking history	Medium ¹	C
Obesity (BMI >30 kg/m ²)	Medium ¹	C
Risk level		

VEGF inhibitors (MAB or tki)

Table 4 Baseline cardiovascular risk stratification proforma for vascular endothelial growth factor

Risk factor	Score	Level of evidence
Previous cardiovascular disease		
Heart failure or cardiomyopathy	Very high	C
Arterial vascular disease (IHD, PCI, CABG, stable angina, TIA, stroke, PVD)	Very high	C
Venous thrombosis (DVT or PE)	High	C
Baseline LVEF <50%	High	C
Borderline LVEF 50–54%	Medium ²	C
QTc ≥480 ms	High	C
450 ms ≤ QTc <480 ms (men) 460 ms ≤ QTc <480 ms (women)	Medium ²	C
Arrhythmia ^a	Medium ²	C
Cardiac biomarkers (where available)		
Elevated baseline troponin ^b	Medium ¹	C
Elevated baseline BNP or NT-proBNP ^b	Medium ¹	C
Demographic and cardiovascular risk factors		
Age ≥75 years	High	C
Age 65–74 years	Medium ¹	C
Hypertension ^c	High	C
Diabetes mellitus ^d	Medium ¹	C
Hyperlipidaemia ^e	Medium ¹	C
Chronic kidney disease ^f	Medium ¹	C
Proteinuria	Medium ¹	C
Previous cardiotoxic cancer treatment		
Prior anthracycline exposure	High	C
Prior radiotherapy to left chest or mediastinum	Medium ¹	C
Lifestyle risk factors		
Current smoker or significant smoking history	Medium ¹	C
Obesity (BMI >30 kg/m ²)	Medium ¹	C
Risk level		



Età	VEGF	Antraciclina e	HER-2	BCR-ABL	IMI	RAF- MEK
>80	ALTO	ALTO	ALTO	ALTO	ALTO	MEDIO
>75	ALTO	MEDIO	MEDIO	ALTO	ALTO	MEDIO
>70	MEDIO	MEDIO	MEDIO	MEDIO	MEDIO	MEDIO
>65	MEDIO	MEDIO	MEDIO	MEDIO	MEDIO	MEDIO
>60	-	-	-	MEDIO	-	-

Quindi anziano equivale ad alto rischio?

Alto rischio CV = referral
precoce a cardiologo



SI; il cardiologo troverà i pazienti
che sono davvero ad alto rischio

Alto rischio CV = maggior rischio
di sottotrattamento



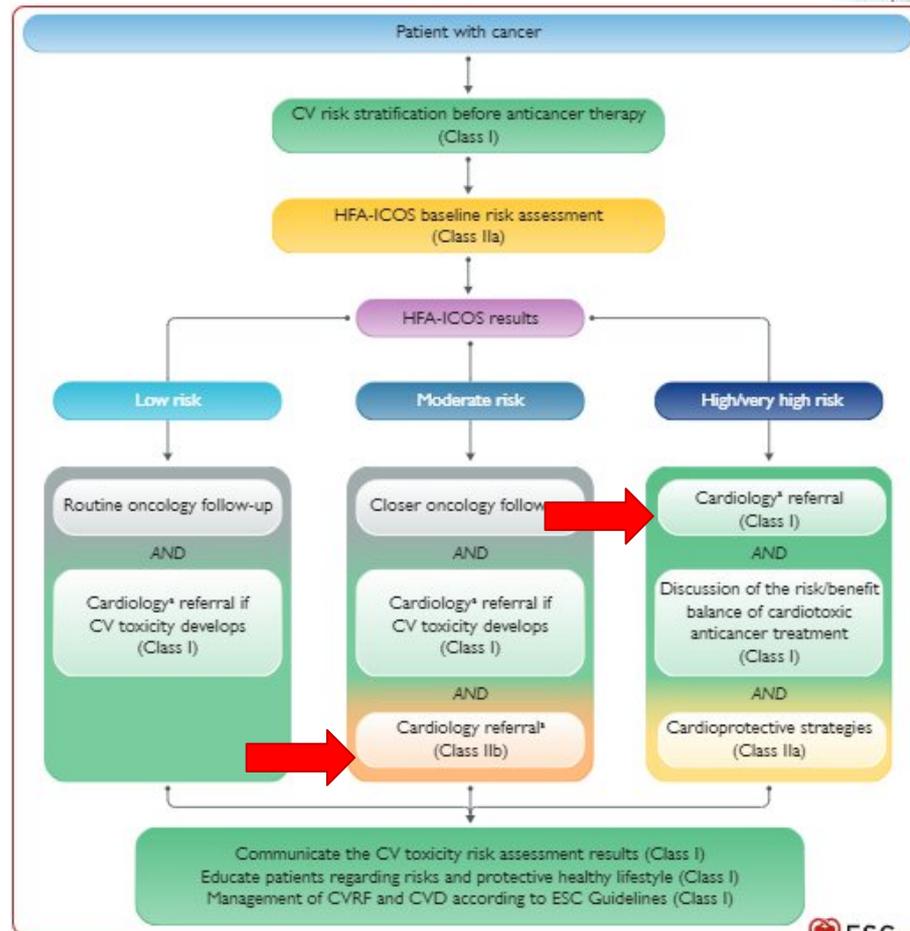
NO! Il cardiologo deve ottimizzare
il rischio, permettere le cure e
impostare un follow-up

Rischio CV baseline (pre trattamenti)

decidere chi deve essere
inviato a

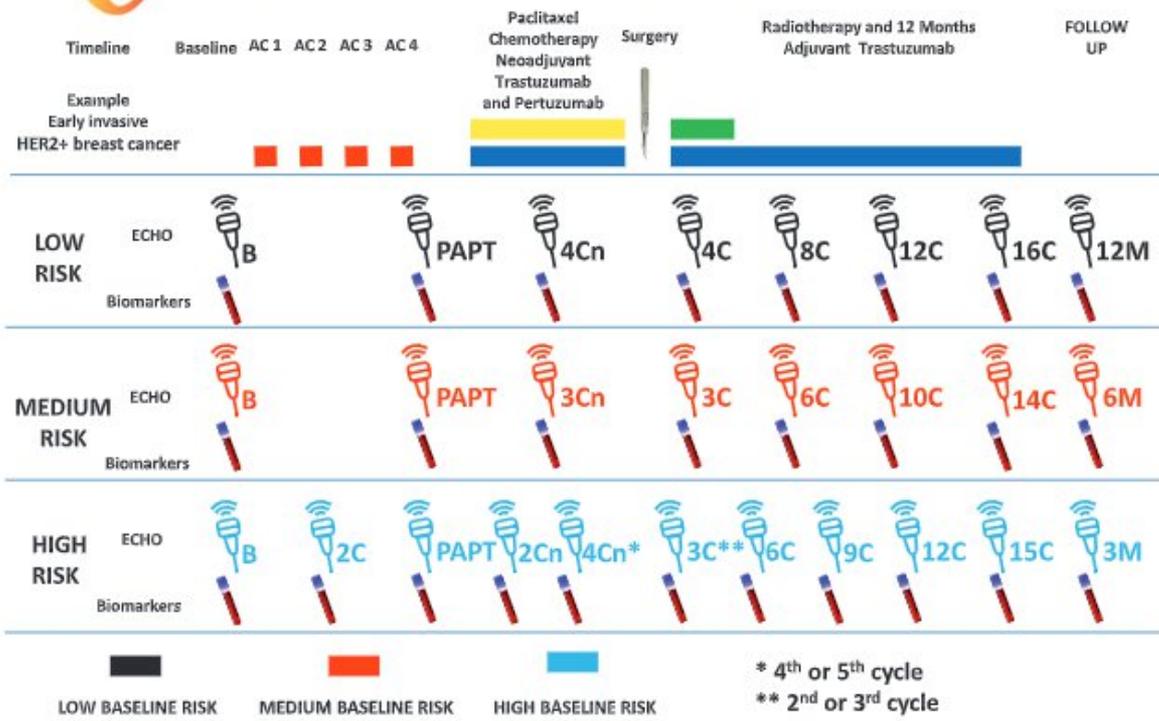
- Cardiologi
- Cardio-oncologi (per chi ce l'ha)

Alexander R Lyon, et al. - ESC Scientific Document Group, 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC), *European Heart Journal*, 2022



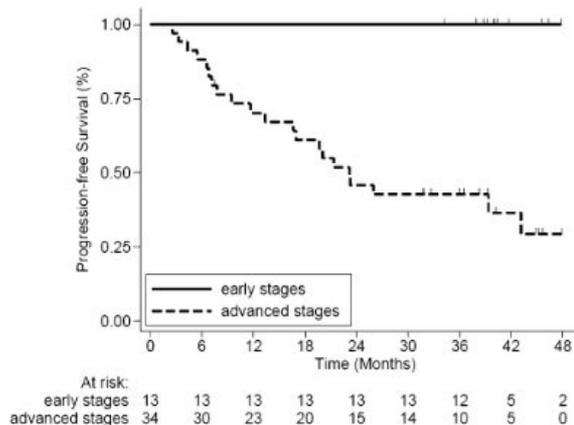


Trastuzumab Surveillance Protocol





Bleomycin, vinblastine and dacarbazine combined with nonpegylated liposomal doxorubicin (MBVD) in elderly (≥70 years) or cardiopathic patients with Hodgkin lymphoma: a phase-II study from Fondazione Italiana Linfomi (FIL). Salvi, F. et al. (2019) - Leukemia & lymphoma



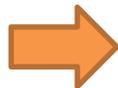
Early stage: nessun evento

Advanced stage:

3 morti trattamento relate

2 polmoniti

1 «heart attack»



2 morti cardiache tardive (una HF e una «heart attack»)

Totale 3/47 (6.4%) nel follow-up (mediana 40 m)

Overall, according to the co-primary endpoint, cardiotoxicity was observed in 2 patients (4.3%) (maximum and acceptable cardiotoxicity threshold for safety 20% and 5%, respectively), including one case with LVEF reduction of 15% (CTCAE grade 2) after six cycles and one fatal cardiac ischemia. This patient was a 76-year-old woman with a medical history of diabetes mellitus, arterial hypertension and cardiac comorbidity. She was admitted to the hospital for atrial arrhythmia and congestive heart failure after the administration of the fourth cycle and died a few days



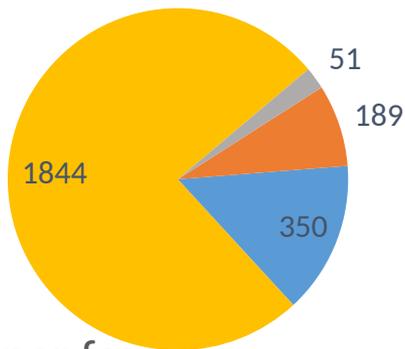
Morti CV in over 70 in Italia (2019)
 Circa 2000 per 100000 abitanti/anno (2% anno)

Rischio evidentemente maggiore per pazienti a rischio CV elevato, con comorbidità, e a maggiore età

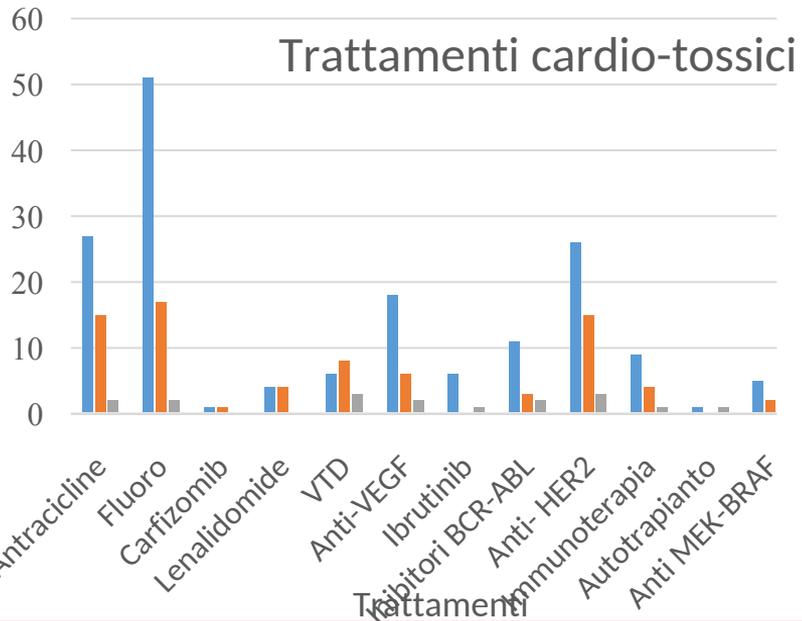
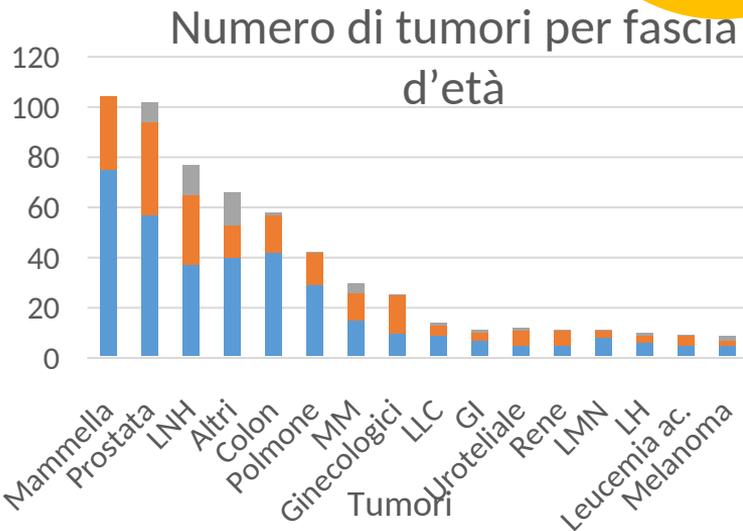
ourworldindata.org



Su **2434** pz visitati nel biennio 2018-2019, **590** avevano età ≥ 75 anni



Su 590 pz, **304** sono stati trattati con chemioterapia cardio-tossica



Comorbilità CV
baseline

Età	Tot pz.	IMA	CAD	PAOD	HF	LVD FE40-50	LVD <40	AF	BPCO	IRC	TEP
TOT	590	43 (7,3%)	58 (9,8%)	26 (4,4%)	13 (2,2%)	9 (1,5%)	3 (0,5%)	75 (12,7%)	38 (6,4%)	38 (6,4%)	29 (4,1%)
75-79	350	23 (6,6%)	34 (9,7%)	20 (5,7%)	9 (2,6%)	5 (1,4%)	2 (0,6%)	32 (9,1%)	23 (6,6%)	15 (4,2%)	11 (3,1%)
80-84	189	16 (8,5%)	17 (8,9%)	5 (2,6%)	3 (1,6%)	4 (2,1%)	0	34 (17,9%)	11 (5,8%)	18 (9,5%)	9 (4,7%)
≥ 85 anni	51	4 (7,8%)	7 (13,7%)	1 (1,9%)	1 (1,9%)	0	1 (1,9%)	9 (17,6%)	4 (7,8%)	5 (9,8%)	4 (7,8%)

FDR baseline

Età	Tot Pz.	IPT	Fumo attivo	ex-fumo	dislipide mie	DM2	<3 FDR	≥ 3 FDR
TOT	590	405 (68,6%)	42 (7,1%)	206 (34,9%)	184 (31,2%)	94 (15,9%)	491 (83,2%)	99 (16,8%)
75-79	350	233 (66,6%)	27 (7,7%)	132 (37,7%)	118 (33,7%)	62 (17,7%)	283 (80,9%)	67 (19,1%)
80-84	189	137 (72,5%)	14 (7,4%)	60 (31,7%)	57 (30,2%)	27 (14,3%)	163 (86,2%)	26 (13,7%)
≥ 85 anni	51	35 (68,6%)	1 (1,9%)	14 (27,5%)	9 (17,6%)	5 (9,8%)	45 (88,2%)	6 (11,8%)

Androgen deprivation ICOS Proforma

Table 8 Baseline cardiovascular risk stratification proforma for androgen deprivation therapies including gonadotrophin-releasing hormone agonists (goserelin, leuprolide) and anti-androgen therapies (abiraterone) for prostate cancer

Clinical risk score ^a	Score
Known pre-existing cardiovascular disease (CVD) ^b or CVD 10-year risk score $\geq 20\%$	High
CVD 10-year risk score $\geq 10\%$ to $< 20\%$	Medium
CVD 10-year risk score $< 10\%$	Low

CVD, cardiovascular disease.

Risk factors and variables required: age, gender, ethnic group, height, weight, social class indicator (Townsend quintile), smoking status (current, ex- or non-smoker), total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure (mmHg), diabetes status (yes/no), family history of premature CVD (before 60 years) (yes/no), chronic kidney disease (yes/no), atrial fibrillation (yes/no), systemic inflammatory disease (e.g. rheumatoid arthritis, psoriasis) (yes/no).

^aFor validated CVD risk scores, see Table 9.

^bPrior symptomatic coronary artery disease, carotid artery disease or peripheral artery disease, e.g. stable angina, acute myocardial infarction, transient ischaemic attack/stroke, ischaemic claudication.

Cardiovascular risk profile and events before and after treatment with anti-VEGF drugs in the setting of a structured cardio-oncologic program

Giacomo Tini^{1,2}, Matteo Sarocchi¹, Davide Sirello^{1,2}, Roberto Murialdo³, Giuseppe Fornarini⁴, Giulia Buzzatti⁵, Francesco Boccardo^{2,6}, Eleonora Arboscello⁷, Italo Porto^{1,2}, Pietro Ameri^{1,2*}, and Paolo Spallarossa¹

significant number of cases, CV risk factors were not adequately controlled: 26.7% of the hypertensive patients had BP values not reaching the recommended goals^{6,7} and were given indications to optimize anti-hypertensive therapy; 56.8% of those with dyslipidaemia had serum lipid values not on target⁸ and/or were not treated. At baseline evaluation, mean

Il rischio cardiovascolare generale è fondamentale
Molti pazienti fumatori
Molti pazienti fuori target ldl
Molti pazienti non conoscono la loro PA né i valori normali





Considerazioni

Nella nostra esperienza il 25% della cardio-oncologia è dell'anziano (>75 anni)

Molti hanno fattori di rischio

L'anziano come il paziente ad alto rischio ha ricevuto insufficienti attenzioni

- Entità del rischio assoluta
- Efficacia della protezione

La valutazione cardio-oncologica è volta a evitare il sotto-trattamento

Anche nel paziente unfit/frail distinguere la componente cardiovascolare (NYHA &C) da quella extra (per es cancro-relata) aiuta una più obiettiva valutazione geriatrica e oncologica.