



ANMCO/AIOM/AICO Consensus Document on clinical and management pathways of cardio-oncology: executive summary

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Cardiovascular disease and cancer are leading causes of death. Both diseases share the same risk factors and, having the highest incidence and prevalence in the elderly, they often coexist in the same individual. Furthermore, the enhanced survival of cancer patients registered in the last decades and linked to early diagnosis and improvement of care, not infrequently exposes them to the appearance of ominous cardiovascular complications due to the deleterious effects of cancer treatment on the heart and circulatory system. The above considerations have led to the development of a new branch of clinical cardiology based on the principles of multidisciplinary collaboration between cardiologists and oncologists: Cardio-oncology, which aims to find solutions to the prevention, monitoring, diagnosis and treatment of heart damage induced by cancer care in order to pursue, in the individual patient, the best possible care for cancer while minimizing the risk of cardiac toxicity. In this consensus document we provide practical recommendations on how to assess, monitor, treat and supervise the candidate or patient treated with potentially cardiotoxic cancer therapy in order to treat cancer and protect the heart at all stages of the oncological disease.

Cardiovascular diseases and cancer often share the same risk factors and can coexist in the same individual. Such possibility is amplified by the deleterious effects of cancer treatment on the heart. The above considerations have led to the development of a new branch of clinical cardiology, based on multidisciplinary collaboration between cardiologist and oncologist: the cardio-oncology. It aims to prevent, monitor, and treat heart damages induced by cancer therapies in order to achieve the most effective cancer treatment, while minimizing the risk of cardiac toxicity. In this paper, we provide practical recommendations on how to assess, monitor, treat and supervise patients treated with potential cardiotoxic cancer therapies.

Introduction

Cardiovascular (CV) disease and cancer are the cause of about two-thirds of all deaths worldwide.¹ Due to the progressive aging of the population the eventuality that a same individual may be affected by both, CV and cancer, is not uncommon.² The association, indeed, is not casual, cancer and heart diseases may share the same risk factors,³ and such chance is amplified by cardiovascular complication of oncologic therapy that can lead to premature morbidity and death of cancer survivors.⁴ The above considerations have led to the development of a new branch of clinical cardiology: the cardio-oncology,⁵ a discipline based on the collaboration among cardiologists, oncologists and other medical specialists in order to find solutions for the prevention, monitoring, diagnosis and treatment of heart damage before, during and after antitumour treatments (*Figure 1*). In this Executive Summary we point out the major key points in order to achieve the most effective cancer treatment, while minimizing the risk of cardiac toxicity.

The assessment of the cardiovascular risk

Many oncologic drugs have cardiotoxic effects⁴ (*Table 1*) often exacerbated by the presence of a pre-existing heart disease (clinical or subclinical) or by the presence of traditional CV risk factors.⁴ The estimation of CV risk profile of patients (*Table 2*) is valuable in cardio-oncology and should be integrated with data related to tumour treatment, in

order to improve the choice on the most appropriate chemotherapy protocol and on the best cardio-protective therapy as well as to perform the most appropriate monitoring measures to schedule the follow-up. The CV risk factors should be treated with appropriate primary and secondary prevention measures according with the most recent guidelines on cardiovascular prevention of the European Society of Cardiology (ESC).⁶

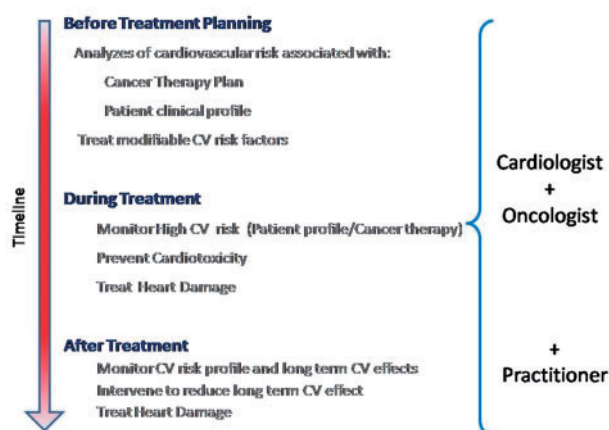


Figure 1 The collaborative model in cardio-oncology. The realization of a management strategy to effectively treat cancer and minimize the risk of cardiac damage provides for close multidisciplinary collaboration between the different actors involved in patient management. The cooperation is particularly necessary in the presence of a patient with a structural heart disease or a high CV risk and with potentially cardiotoxic care plan.

Table 1 Antineoplastic agents and their cardiotoxic effect⁶

Class	Indication*	Incidence					
Drug		Arrhythmias	QT elongation	Systolic dysfunction	Hypertension	Myocardial ischaemia	Thrombo-embolism
Anthracyclines							
Daunorubicin	Leukemia	++/ +++	✓	+	—	—	—
Adriamycin	Breast, Lymphomas, Sarcomas	+ / ++	✓	++ / +++	—	—	✓
Liposomal adriamycin	Lymphomas, Sarcomas	+	✓		—	+ / ++ / +++	
Epirubicin	Breast, Stomach	—	✓	+ / ++	—	—	✓
Idarubicin	Leukemia	++ / +++	✓	++ / +++	—	—	✓
Mitoxantrone	Leukemia	++ / +++	✓	++ / +++	++	++	—
Alkylating agents							
Cisplatin	Bladder, HNC, Lung, Ovary	✓	✓	✓	✓	✓	++
Cyclophosphamide	Hemat. Breast	—	—	✓	—	—	+
Ifosfamide	Cervix Sarcomas	✓	—	+++	—	—	+
Antimicrotubules agents							
Docetaxel	Breast Lung	+ / ++	✓	++	++	++	✓
Nab-Paclitaxel	Breast Pancreas	+ / ++	✓	—	—	—	+
Paclitaxel	Breast Lung	++	✓	+	—	+	—
Antimetabolites							
Capecitabine	Colon-Rectum Breast	✓	✓	✓	—	++	+ / ++
5-Fluorouracil	Gastrointestinal	✓	✓	+	—	++ / +++	✓
Hormone therapy							
Abiraterone	Prostate	++	—	++	++ / +++	++	—
Anastrozole	Breast	—	—	—	++ / +++	++	++
Exemestane	Breast	—	—	—		++	+
Letrozole	Breast	—	—	—	++	++ / +++	++
Tamoxifen	Breast	—	✓	—	++ / +++	++	++
Target therapy with monoclonal antibody							
Bevacizumab	Colon-Rectum Breast	++	✓	+ / ++	++ / +++	+ / ++	++ / +++
Brentuximab	Lymphomas	—	—	—	—	+	++
Cetuximab	Colon-Rectum HNC	++	—	✓	++	✓	+ / ++
Ipilimumab	Melanoma	—	—	—	—	—	—
Panitumumab	Colon-Rectum	✓	—	—	++	++	+
Pertuzumab	Breast	—	—	++	—	—	—
Rituximab	Hemat.	✓	—	—	++	++	++ / +++
Trastuzumab	Breast Stomach	++	—	++ / +++	++	—	+ / ++
Target therapy with small molecules							
Bortezomib	Multiple myeloma	+	—	+ / ++	+	+	+
Dasatinib (TKI)	Leukemia	++ / +++	+ / ++	++	++	++	+ / ++
Erlotinib (TKI)	Lung	✓	—	—	—	++	++
Gefitinib (TKI)	Lung	✓	✓	—	—	+ / ++	✓
Imatinib (TKI)	CMC	—	—	+ / ++	—	+++	+
Lapatinib (TKI)	Breast	✓	+++	++	—	—	—
Nilotinib (TKI)	CMC	++	++	++	++	✓	+
Pazopanib (TKI)	RCC	—	—	+	+++	+ / ++	++
Sorafenib (TKI)	RCC, HCC	+	✓	+	+++	++	++
Sunitinib (TKI)	GIST, RCC	+	+	++ / +++	+++	++	+ / ++
Vemurafenib (TKI)	Melanoma	++	✓	+	++	++	++
Miscellanea							
Everolimus	RCC	—	—	++	++	—	+
Lenalidomide	Multiple myeloma	+ / ++	+	++	++	++	++ / +++
Temsirolimus	RCC	—	✓	—	++	+++	++

*. Selected examples on the frequency of use of the drug; +++, >10%; ++, 1-10%; +, <1% or rare; ✓, observed but the precise incidence has not been well established; —, complication not reported; CML, chronic myeloid leukemia; GIST, gastrointestinal stromal tumour; HCC, hepatocellular carcinoma; Emat., haematological; HF, heart failure; HNC, cancer of the head and neck; RCC, carcinoma of the kidney; TKI, tyrosine kinase inhibitor.

Table 2 Patient-related risk factors for cardiotoxicity

What to look	What to evaluate	How to treat
Known heart disease	Present/absent ^a	Implement primary/secondary prevention measures provided for by the Guidelines
Prior exposure to cardiotoxic chemotherapy and/or mediastinal radiotherapy	Present/absent ^b	In case of exposure in asymptomatic patient evaluate the cardiovascular status (ventricular function, silent ischaemia, valves disease)
Smoke	Pack/year ^c	Quit
Alcohol consumption	Daily Units	Abstinence or moderate use (1-4 U/die)
Physical activity	Weekly hours	Encourage mild to moderate aerobic activity (at least 3-5 h/week)
Blood pressure	High blood pressure	search ventricular hypertrophy Give priority to drugs with proven cardioprotective action (ace-i/ARBs, beta-blockers)
Obesity	Calculate body mass index	weight reduction with the Mediterranean diet
High blood sugar	Post-prandial glycaemia (2 h) or glycated haemoglobin and blood glucose ≤ 125 mg/dL but > 100 mg/dL	Implement dietary program and exercise when carbohydrate intolerance, encourage the use of metformin in the case of type II diabetes
Abdominal circumference ^d	Establish whether there is metabolic syndrome	Implement dietary program and exercise, treatment of dyslipidaemia and high blood pressure
Lipid profile	Total cholesterol, HDL cholesterol, triglycerides	Implement dietary program and exercise, statins
Renal function ^e	Creatinine, eGFR	Low-protein, low-salt diet, treat high blood pressure and dyslipidaemia

^aDefine the type, severity and clinical stability in relation to the oncology care program.

^b'Life span' threshold of high-risk: prior anthracyclines exposure (adriamycin 250-300 mg/m² epirubicin 600-800 mg/m); radiation exposure (35-50 Gy). In the case of radiation define whether he was involved the left hemithorax.

^cIs obtained by multiplying the number of cigarette packs (20 cigarettes) smoked per day by the number of years of smoking.

^d >102 cm men; >90 cm in women.

^eRenal dysfunction = eGFR <60 ml/min.

Heart failure

Heart failure (HF) is a very common complication of anti-neoplastic treatments and may occur with several classes of anticancer drugs⁷⁻⁹ (Table 1). Table 3 shows the risk factors for anthracyclines cardiotoxicity that may lead also to late onset cardiomyopathy.^{10,11} Other conventional chemotherapies, cyclophosphamide, cisplatin, ifosfamide, and taxanes (paclitaxel and docetaxel), can rarely induce left ventricular dysfunction (LVD) and HF. Immunotherapies and targeted therapies (Table 1) can, also, cause LVD and HF. Moreover, concomitant use of anthracyclines with trastuzumab, a monoclonal antibody directed against the receptor HER2/ErbB2, especially in cancer patients with high CV risk, may lead to severe cardiotoxicity effects.^{7-9,12,13} Nevertheless, trastuzumab-related cardiomyopathy is not dependent on cumulative dose and is considered to be reversible upon treatment discontinuation and proper therapy.⁹ The cardiotoxicity risk of other anti-HER2/ErbB2 targeted agents (lapatinib, pertuzumab, and trastuzumab-emtansine) appears to be similar to that of trastuzumab.⁹

Vascular endothelial growth factor (VEGF) inhibitors can cause reversible or irreversible cardiac side effects: arterial hypertension is the most frequent, with potential LVD and HF.

Management

Cardiotoxic cardiomyopathy is difficult to treat and has a relatively poor prognosis if not promptly diagnosed.¹⁴ Among

the imaging techniques, a predominant role is played by echocardiography, a non-invasive, repeatable, available and relatively inexpensive technique.⁹ The ejection fraction (EF) is the echocardiographic parameter most frequently used to monitor heart health. Significant declines of EF often may occur at a later time with irreversible cardiac damage. One of the aims of clinical research is to find the best technique able to identify the early cardiac damage before it produces alterations of the common ventricular contractility indexes, and then before the cardiac damage becomes irreversible (Table 4). In the recent years, Global Longitudinal Strain (GLS) technique, assessed using automated speckle-tracking echocardiography (STE), has emerged for detecting and quantifying LVD. A drop of 10% from baseline is very largely abnormal and may represent subclinical dysfunction in order to consider cardioprotection also in patients without the classic criteria of cardiotoxicity (LVEF $< 50\%$). It has been largely demonstrated that this technique is very promising to monitor the effects of cardioprotection.

Biomarkers (Table 5), also, may be used as 'red flags' to encourage a close clinical and instrumental monitoring and treatment. The same biomarker assay may be used for continued screening throughout the treatment pathway and substantial increases during follow-up may anticipate asymptomatic LVD in high CV risk patient treated with potentially cardiotoxic chemotherapy. Nevertheless at present the evidence to establish the interpretation of subtle variation is insufficient and their role as exclusive

Table 3 Risk factors of anthracyclines cardiotoxicity

Risk factor	
Cumulative dose (life-span)	Total cumulative dose (Adriamycin > 450 mg/m ² ; epirubicin > 900 mg/m ²) markedly increases the risk in the long-term cardiotoxicity
Duration of follow-up	The risk increases with prolonged survival for doses > 250 mg/m ²
Rate of administration	The risk of acute cardiotoxicity is lower with slow rate of infusion
Individual dose	Single high doses increase the risk of late onset toxicity
Type of anthracycline	The liposomal anthracyclines are less cardiotoxicity
Radiotherapy	Prior or concomitant administration (>30 Gy) increases the risk of cardiotoxicity
Complementary chemotherapy	Trastuzumab, bevacizumab, paclitaxel, alkylating agents (cyclophosphamide, ifosfamide, melphalan), bleomycin, vincristine, paclitaxel, docetaxel
Pre-existing cardiovascular risk factors	Hypertension, ischaemic heart disease, valvular heart disease, previous cardiotoxic treatments
Comorbidity	Diabetes mellitus, chronic obstructive pulmonary disease, renal dysfunction, liver failure, obesity, dysthyroidism, electrolyte disorders, sepsis
Age	Young and old are at greatest risk
Sex	Women are at greater risk than men
Additional factors	Trisomy 21 and African American race are at greater risk

Table 4 Summary table of the instrumental parameters used to identify the damage from chemotherapy

Method used	Parameter	Diagnostic values for cardiotoxicity	Limits
Echocardiography	Ejection fraction (EF)	<ul style="list-style-type: none"> * Decrease > 5% with EF < 55% if symptomatic patient for heart failure (HF) * Decrease > 10% with EF < 55% if asymptomatic patient 	<ul style="list-style-type: none"> * Image quality (better with ultrasound contrast agent) * Dependence on the haemodynamic state * Intra- and inter-operator variability (better with 3D-echo) * Late and irreversible alterations
Dobutamine stress-echo	EF Fractional shortening (FS)	* Reduction of EF and/or FS during pharmacological stress	* Consistent results but from small and not confirmed studies
Doppler Echocardiography	Diastolic parameters: isovolumetric relaxation time (IVRT), deceleration time (DT), E, e', E/A ratio,	* Diastolic dysfunction (↑ IVRT and DT, ↓ E, e' and E/A ratio)	<ul style="list-style-type: none"> * Discordant data on the predictive power of future dysfunction * Not recommended for monitoring
Tissue Doppler Imaging (TDI)	Mitral annulus velocity (s') septal and lateral	* Reduction below 15 cm/sec (septal) and 20 cm/sec (lateral)	<ul style="list-style-type: none"> * Discordant data between different studies * Frequent reduction of s' in pts with prior chemotherapy, without development of HF
Two-dimensional Speckle Tracking echocardiography	Global longitudinal strain	* Reduction of > 15% from baseline within days after chemotherapy seems to predict future decline in EF	<ul style="list-style-type: none"> * Need for dedicated software * Results still to be confirmed on a large scale
Cardiac magnetic resonance (CMR), dynamic sequences without contrast	LV and RV volumes and EF	* Improved accuracy and reproducibility in identifying drops in EF	<ul style="list-style-type: none"> * Costs * Availability on the territory
CMR, delayed sequences after contrast agent (gadolinium)	Early (oedema) and late (fibrosis) enhancement	<ul style="list-style-type: none"> * Intramyocardial oedema seen during therapy with trastuzumab and ↓ FE * Fibrosis is associated with poor prognosis 	* Results regarding prognostic significance of oedema and fibrosis to be confirmed on a large scale

Table 5 Biomarkers and risk stratification

Marker type	Population studied	Findings and observations
TnT, TnI, hsTnT	Anthracyclines: baseline measurement, at the end of the infusion, and one month after chemotherapy	* High predictive value (mostly negative) in the high-dose anthracyclines * Maybe poor prognostic factor in medium and low doses
TnT, TnI, hsTnT	Trastuzumab for metastatic breast cancer: baseline survey, 2 and 4 months after starting treatment	* It seems to anticipate about 2 months the development of systolic dysfunction * Increased positive predictive value when combined with declining global longitudinal strain * Results to be confirmed in larger studies
BPN, Nt-proBNP	Anthracyclines (breast cancer): before and after treatment	* A > 36% increase from baseline seems to correlate with LV systolic dysfunction * Mixed results in different studies
BNP, Nt-proBNP	Trastuzumab	* Few studies, mixed results

Table 6 Strategies to control the risk of cardiotoxicity

Type of strategy	Advantages	Only retrospective studies
Weekly infusions (instead of three times a week)	Lower blood peaks, observed incidence of heart failure 0.8% (vs. 2.9% with traditional scheme)	Only retrospective studies
Prolonged infusion (>6 h) instead of rapid bolus	Lower blood peaks, reduced incidence of heart failure	Need for central venous access, with increase of costs, preparation time and care, risk of infection
Epirubicin	Better tolerance compared with doxorubicin.	Higher costs of doxorubicin
Liposomal anthracyclines (pegylated or non-pegylated)	Lower volume of distribution, with greater concentration on the neoplastic tissue less cardiotoxicity	* Not available studies directly comparing with free doxorubicin.
Iron chelating agents (dexrazoxane)	Protective effect on acute cardiotoxicity Currently only indicated for patients with metastatic breast cancer previously treated with high doses of anthracyclines	* Not available data on the protective effect of late toxicity * Equivocal increase of seconds in the long run tumours

method for routinely surveillance of cardiac damage is not clearly ascertained.

Strategies for reducing cardiotoxicity

In the absence of definite treatments that can reverse the anthracyclines-related myocardial damage, it is important to identify new treatment strategies that prevent or minimize the potential cardiotoxic side effects (*Table 6*), especially in high risk patients (*Table 3*) that require a strict control of traditional CV risk factor.

Ischaemic heart disease

Radiation therapy as well as many cancer drugs can induce myocardial ischaemia^{4,7,9} (*Tables 1 and 7*).

Fluoropyrimidine and capecitabine

Asymptomatic ST-segment changes on ECG represents the most frequent cardiotoxic manifestation (55%). Chest pain

with or without ST-segment changes is the common clinical complaint (45%) and evolution in acute coronary syndrome may occur. Patients should be closely monitored for myocardial ischaemia using regular ECG. The symptoms usually occur within the first 72 h of 5-fluorouracil (5-FU) infusion and in the first 6 days of initiation in the case of oral administration of capecitabine.¹⁵ Occasionally, 5-FU and Capecitabine toxicity appear as acute heart failure and Tako-tsubo syndrome with LVD, in such case ventricular arrhythmias and sudden death may occur. Ischaemic heart disease can also be a complication of antiangiogenic agents: bevacizumab and tyrosine kinase inhibitors (sunitinib, sorafenib, ponatinib, axitinib, pazopanib, regorafenib).⁹ Coronary artery disease may be a late complication of high radiation doses to mediastinum.

Management

In the case of fluoropyrimidine toxicity, chemotherapy should be stopped and patients hospitalized in coronary

intensive care if acute coronary syndrome is suspected. The administration of non-dihydropyridine calcium channel blockers (verapamil or diltiazem) and nitrates may be indicated for the frequent occurrence of coronary spasm. If there is an absolute indication on drug rechallenge, the treatment should be performed with half dose and the patients monitored closely. The association of calcium channel blockers therapy may be useful.

Arrhythmias

In cancer patients Heart Rhythm Disturbances (HRD) may be the result of multiple risk factors. Metabolic disorders, electrolyte disturbances, medications (e.g. antihistamines, antiemetic, anti-infective, psychotropic drugs) can affect the appearance of cardiac arrhythmias. Nevertheless, HRD are more frequent with some chemotherapies (Tables 1 and 8). A 12-lead ECG should be recorded and the QT interval, corrected for heart rate with

Table 7 Chemotherapy associated with ischaemia (Modified by 14)

Drug	Incidence
5-Fluorouracil	1-68%
Capecitabine	3-9%
Paclitaxel	<1-5%
Sunitinib/Sorafenib	2.3%
Erlotinib	2.3%
Bevacizumab	0.6-1.7%
Axitinib	1-2%
Pazopanib	2%
Ponatinib	3-20%

Bazett's or Fridericia's formula, should be obtained in all patients at baseline. Treatment should be interrupted or alternative regimens considered if the QTc is >500 ms, QTc prolongation is >60 ms or arrhythmias are present. Factors as hypokalaemia, hypomagnesiemia, extreme bradycardia, and QT-prolonging drugs should be minimized inpatients treated with potential QT-prolonging chemotherapy (Figure 2).

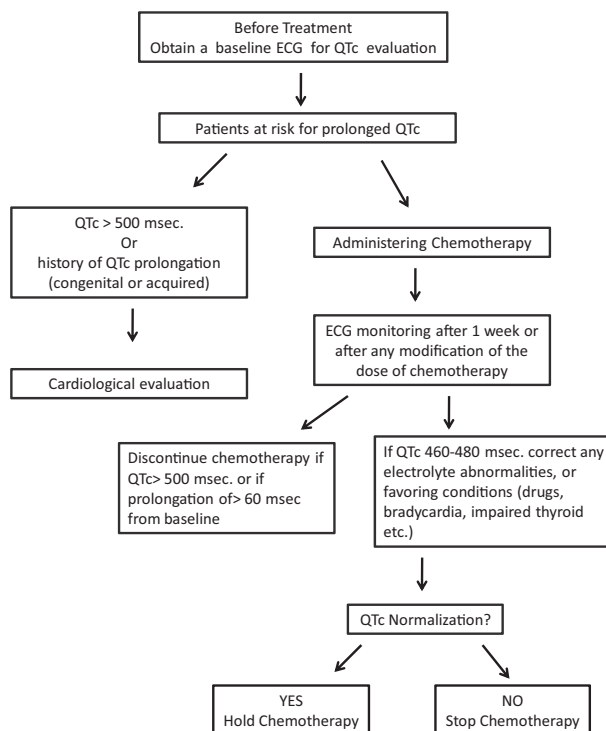


Figure 2 Algorithm for the evaluation and management in the course of chemotherapy with potential effect on the QT.

Table 8 Arrhythmias and related mechanisms of action induced by chemotherapy drugs

Aritmia	Farmaco	Meccanismo d'azione
Bradycardia	Paclitaxel Talidomide	Interference with His-Purkinje system Hyper-reactivity to Cremophor EL (with release of histamine) Vaso-vagal stimulation ↓TNF α and inhibition of the neurons of the nucleus of the vagus Hyperactivity of the parasympathetic system Hypothyroidism
QT prolongation	Arsenic trioxide Tyrosine kinase inhibitors Dasatinib Lapatinib Nilotinib Sunitinib Vandetanib Pazopanib Vemurafenib Vorinostat Anthracyclines	Block of the potassium channels Calcium overload (due to oxidative stress) Apoptosis Fragmentation of DNA Block of the potassium channels (encoded by the HERG gene)
Ventricular fibrillation	Capecitabine	Coronary artery spasmKounis Syndrome

Table 9 Risk factors and biomarkers associated with thrombosis in cancer

Cancer-related factors	Treatment-related factors	Patient-related factors	Biomarkers
Primary site of Tumour (pancreas, brain, stomach, kidney, lung, lymphoma, myeloma)	Major Surgery (abdomen, pelvis)	Old Age	Platelet Count ≥ 350000 ,
Advanced Stage (metastatic)	Chemotherapy	Gender (Female > Male)	White Blood Cells count > 11000
Histology (>adenocarcinoma)	Antioangiogenic Agents (Lenalidomide, Talidomide, Bevacizumab)	African ethnicity	Haemoglobin (Hb) <10 g/dL
Initial period after diagnosis (3-6 months)	Hormone Therapy	Comorbidities (infections, renal dysfunction, pulmonary disease, atherosclerotic disease)	high levels of D-dimer, high level of soluble P-selectin, high level of C-reactive protein
	erythropoiesis-stimulating factors (ESA), transfusion; central venous catheters (CVC); duration of surgery > 30', radiotherapy (RT)	Inherited prothrombotic Mutations	
		Obesity	
		History of thrombo-embolic disease	
		Poor performance status (PPS)	

Arterial hypertension

Hypertension is a frequent co-morbidity in patients with cancer and may be worsened or newly induced by steroids or non-steroid anti inflammatory drugs frequently used in oncology. Antiangiogenic agents (*Table 1*) can induce hypertension and degenerate to related heart complications (i.e. heart failure, myocardial ischaemia). ACE inhibitors or ARBs, beta-blockers and dihydropyridine calcium channel blockers are the antihypertensive drugs of choice. Non-dihydropyridine calcium channel blockers should preferably be avoided due to drug interactions.

Thrombo-embolic disease

Thrombo-embolism often complicates the course of cancer and recognizes different aetiological moments (*Table 9*). The arterial thrombotic events (ETA) in cancer can occur in case of treatment with anti-angiogenic drugs, cisplatin, VEGF inhibitors, and hormonal therapies. Ischaemia/myocardial infarction is the most common clinical manifestation. The pro-thrombotic state may facilitate embolic events secondary to atrial fibrillation. The most frequent thrombo-embolic complications in cancer patients are venous thrombo-embolism (VTE) with deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is the second cause of death in cancer patients. It may affect up to 20% of hospitalized patients and is frequently undiagnosed. A four weeks antithrombotic therapy with low molecular weight heparin (LMWH) is currently recommended for VTE prophylaxis by consensus guidelines.⁹ In the case of major surgery, systematic prophylaxis for VTE in outpatient admitted for chemotherapy is not recommended and the decision should be individualized. In stable patients LMWH given over a period of 3-6 months is the first choice for TVE therapy in cancer patients. At the moment we do not have enough data to support the use of fondaparinux or new oral anticoagulants (NOAC) for the initial treatment of acute VTE in patients with cancer. We are waiting the results of Hokusai VTE-cancer to know if edoxaban is similar to

dalteparin in preventing recurrence of acute VTE following and initial index in cancer subjects.¹⁵ Different NOACs may differ because of potential drug interactions and sensitivity to renal or hepatic dysfunction. The use of vitamin K antagonists (VKA) in cancer patients is complicated; difficulties in maintaining a therapeutic International Normalised Ratio (INR) occur due to a variety of reasons such as drug interactions, unpredictable bioavailability, vomiting, malnutrition or diarrhea, poor compliance for repeated laboratory tests.

Surveillance in the follow-up

Cancer patients follow-up is critical for the prevention and treatment of possible late cardiovascular complications (*Table 10*).

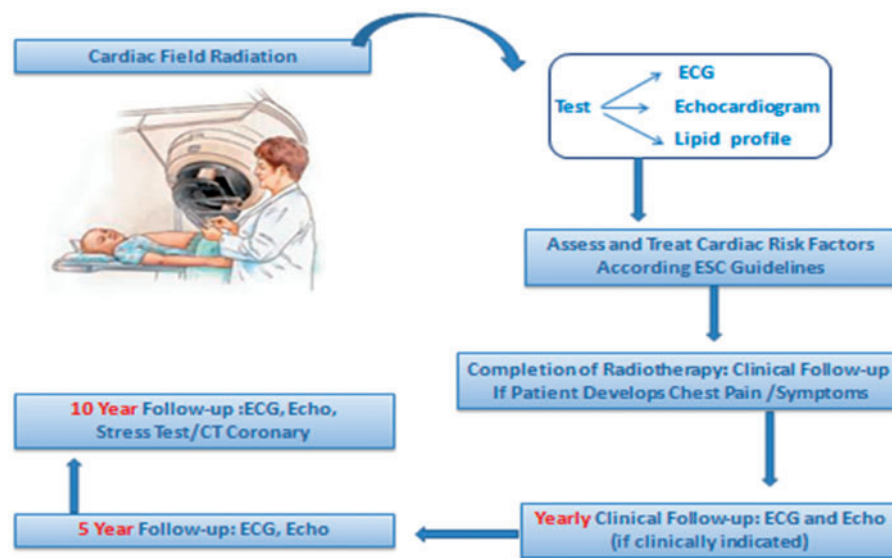
Cancer patients should be aware on the possible cardiovascular risk factors, overall subjects treated with anthracyclines or mediastinal radiotherapy. At 10 years it is mandatory to perform stress test or CT coronary angiography¹⁶ (*Figure 3*). Moreover, patients should be encouraged to a healthy lifestyle. A careful surveillance is often necessary for the patients in long-term hormonal therapy. Tamoxifen may increase the risk of thrombo-embolic complications and aromatase inhibitors have been linked to increased risk of heart disease. The same applies to patients treated with androgen deprivation therapy (ADT) for prostate cancer which are prone to metabolic syndrome, diabetes, accelerated atherosclerosis, and cardiovascular events.

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Table 10 Suggested follow-up and treatment after cancer therapy

Treatment performed	Exams programmed	Associated risk factors
Anthracyclines, particularly if: <ul style="list-style-type: none"> • Female • Age <15 years or > 60 years • Dose (Doxorubicin > 240 mg/mq; Epirubicin > 360 mg/mq) 	Echocardiogram At 6-12 month of follow-up, after completion of chemotherapy Every 1-5 years, depending on the risk profile	Hypertension Dyslipidaemia Diabetes mellitus Obesity Sedentary Smoke Alcohol consumption
Target therapy \pm Taxanes	Yearly for 5 years after the conclusion of therapy. Thereafter every 5 years	
Hormone therapy	Clinical follow-up	Kidney failure
Radiation therapy to the chest/mediastinal if involved the left hemithorax and/or total radiation in the cardiac area ≥ 30 Gy	Echocardiography at 6-12 month of follow-up, then every 1-5 years depending on risk profile Exercise test after 5 years and then every 3-5 years.	
Radiation therapy to the head/neck	Consider Stress-Echocardiography or coronary CT scan Carotid artery Echo-Doppler after 3-5 years Ultrasound thyroid and periodic evaluation of thyroid hormones (FT3, FT4, TSH)	

**Figure 3** Algorithm of patient management during and after radiation.

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Massimiliano, Rasetti Gerardo, Riccio Carmine, Roncon Loris, Rossini Roberta, Ruggieri Maria Pia, Rugolotto Matteo, Sanna Fabiola, Sauro Rosario, Scherillo Marino, Severi Silva, Sicuro Marco, Sisto Francesco, Uguccione Massimo, Urbinati Stefano, Valente Serafina, Vatrano Marco, Vianello Gabriele, Vinci Eugenio, Zuin Guerrino.

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