ACOS Newsletter

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We invite suggestions and contributions from our readers

Newsletter Designed by

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Message from ACOS President (1/2)

Immune Checkpoint Inhibitor induced myocarditis – current recommendations and guidelines

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In August 2021, Emma Matzen and colleagues published regarding seriousness of Immune checkpoint inhibitor-induced myocarditis – in the *Cardio-Oncology* journal volume 7

(https://doi.org/10.1186/s40959-021-00114-x)

There is increasing awareness that ICI-induced myocarditis, is associated with high mortality especially when patients are being treated with ICI combination therapy. But its treatment remains an enigma. Current guidelines are based mainly on expert consensus rather than level one evidence from randomized controlled studies. Today we follow the recommendation of discontinuation ICI therapy and treatment with high-dose corticosteroids. Other management options include the use of antithymocyte globulin, mycophenolate mofetil, infliximab, tacrolimus, betablockers and angiotensin converting enzyme (ACE) inhibitors – the last two indicated only in patients with reduced LVEF. However, the efficacy and safety of treatments for ICI-induced myocarditis have not been evaluated.

Amongst 87 cases with myocarditis induced by ICI, (melanoma = 39; lung cancer = 19; renal cell cancer = 10; and thymoma cancer = 4), 38 (44%) cases, received high-dose steroid treatment alone whereas the other 49 (56%) cases received immunosuppressive agents other than steroid (13 different drugs including alemtuzumab and abatacept).

The median time to onset of symptoms after initiation of ICI was 16 days (range, 1–196 days); cardiotoxic symptoms developed after 2 cycles of ICI (range, 1–13 cycles). A total of 48% of cases were fatal (55% in those treated with high-dose steroids only vs. 43% amongst cases treated with other immunosuppressive agents - antithymocyte globulin (ATG), mycophenolate mofetil, alemtuzumab, infliximab, abatacept, plasmapheresis, tocilizumab, immunoglobulin, rituximab, tacrolimus, methotrexate and cyclophosphamide).

Myocarditis can be categorized according to the histopathologic pattern. In the fulminant phase there is myocyte damage/necrosis that gets substituted by fibrosis during the healing process. Cardiac myocytes may share targeted antigens also seen on malignant tumors, therefore becoming targets of activated T-lymphocytes that infiltrate the myocardium. Myocarditis can lead to cardiovascular complications like arrhythmias, myocardial infarction, heart failure or cardiogenic shock and sudden cardiac death.

Both alemtuzumab and abatacept could benefit patients with ICI-induced myocarditis, since both drugs target T-lymphocytes (which are prominently seen in endomyocardial biopsies of such ICI-induced myocarditis patients). A word of caution - both these agents can also lead to rise of infection and induce autoimmune diseases.

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Message from ACOS President (2/2)

The current ASCO guideline recommend all patients receiving ICIs to be monitored with cardiac biomarkers and ECG at baseline and regular follow up. In case of deterioration, serial ECGs and cardiac biomarker testing are recommended. Echocardiographic evaluation of GLS is necessary because in some cases the LVEF fails to show any change even in the presence of myocarditis. Cardiac MRI and endomyocardial biopsy should be used as appropriate. Management of CTCAE grade 1 myocarditis (elevated cardiac biomarkers without symptoms) and CTCAE grade 2 myocarditis (symptoms after moderate activity) should include prompt discontinuation of ICI treatment plus commencement of oral high-dose corticosteroids (100 mg daily) for 3 days. If there is no improvement, other immunosuppressive agents should be added. For CTCAE grade 3 or 4 myocarditis pulse high-dose corticosteroids IV should be given for 3 days as a first line treatment.

We are still learning how to diagnose and manage ICI induced myocarditis. In the meantime, we can continue to follow guidelines based on scientific rationale and wait for more robust data to follow.

Forthcoming Conferences – with Cardio Oncology component

10th World Heart Congress **Prague, Czech Republic** **23rd & 24th August, 2021**
GCOS 2021 - Virtual **ICOS (International Cardio-Oncology Society)** **30th September, 2021**
Mayo Clinic Cardio-Oncology Update 2021 **Scottsdale, USA** **4th to 6th November, 2021**

Join us for the 45th Indian Cooperative Oncology Network Hybrid Conference on 1st to 3rd October, 2021

Interested participants can fill the google form on the below link

https://tinyurl.com/45thicon

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Echocardiography and Cancer Therapy (1/4)

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Cardiovascular disease and complications are common in patients with cancer or those undergoing treatment for the same. They form the second leading cause of morbidity and mortality in cancer survivors, after cancer itself.

Echocardiography is a basic investigation for evaluation of any cancer patient with a cardiac symptom such as dyspnoea, palpitation, syncope, angina or features of congestive cardiac failure. Additionally, it is also used to predict or prognosticate patients planned for chemotherapy with known cardiotoxic drugs or radiotherapy. Such patients, often undergo repeated echocardiography examinations – as per laid out protocols – to reduce onset or progress of cardiotoxicity.

Ease of performance, relatively low cost, rapidity with which it can be performed, widespread availability and repeatability make transthoracic echocardiography an investigation of choice for cardiac evaluation in cancer patients. Evaluation of ventricular systolic function with measurement of left ventricular ejection fraction (LVEF) has, erstwhile been the gold standard of evaluation of cardiotoxicity. Advanced echocardiography with three-dimensional echo, strain rate etc. not only aid in providing additional information to established parameters for detection of ventricular dysfunction, but also help in predicting cardiac disease before a derangement of the LVEF.

This 2-part article will review the current status of echocardiography in patients with cancer or those undergoing treatment for the same. Part 1 of the article will discuss cardiovascular complications of cancer therapy, defining chemotherapy associated cardiac disease and discussing various components of ventricular systolic dysfunction. Part 2 of the article will discuss the role of echocardiography in defining diastolic dysfunction, coronary artery, pericardial and valvular disease in patients undergoing cancer treatment as well as finally provide a brief overview of newer forms of echocardiographic assessment.

Cardiovascular complications of cancer therapy

Cancer treatment can cause various types of cardiovascular (CV) complications. Cardiotoxicity is related to the mechanism of action of these drugs, the doses administered, the route of administration and most importantly the underlying predisposing factors. The time line of presentation of cardiotoxicity and CV complications can vary from an immediate effect to long term sequelae. The table below summarises a variety of anti-cancer therapies and their associated complications.

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Echocardiography and Cancer Therapy (2/4)

Type of CV toxicity	Anti-Cancer Agents Involved
Myocardial dysfunction and heart failure	Anthracyclines (doxorubicin, idarubicin and epirubicin), anti-HER2 (trastuzumab), VEGF inhibitors, cyclophosphamide, cisplatin, ifosfamide and taxanes (paclitaxel and docetaxel)
Vasospasm or vasoocclusion resulting in angina or myocardial infarction	Fluoropyrimidines (5-FU, capecitabine and gemcitabine), platinum compounds (cisplatin), VEGF inhibitors (bevacizumab, sorafenib and sunitinib) and radiotherapy
Valvular disease	Radiotherapy
Arrhythmias	Anthracyclines, histone deacetylase inhibitors, tyrosine kinase inhibitors (TKIs) (especially vandetanib high incidence of QT prolongation)
Arterial hypertension	VEGF inhibitors
Peripheral vascular disease and stroke	Nilotinib, ponatinib or BCR-ABL tyrosine kinase inhibitors, radiotherapy. L-asparaginase, cisplatin, methotrexate, 5-FU and paclitaxel can cause Raynaud's phenomenon
Pulmonary hypertension	TKI (dasatinib), the TKI imatinib improved haemodynamic in patients with advanced pulmonary arterial hypertension

Role of Echocardiography in Early Diagnosis and Management of Cancer Treatment Related Cardiotoxicity

Echocardiography is a non-invasive and widely available investigation that aids in performing a comprehensive cardiac evaluation in almost all stages of cancer therapy. It is particularly useful in detecting myocardial dysfunction, valvular abnormalities, pulmonary hypertension, pericardial complications and regional wall motion abnormalities related to coronary artery occlusion. Assessment of left ventricular ejection fraction (LVEF) has erstwhile been the commonest mode of evaluation of LV systolic function evaluation. Its objectiveness renders it to be a tool in various guidelines.

Systolic Myocardial Dysfunction

Myocardial dysfunction resulting in a reduction in LV ejection fraction (LVEF) is the most concerning as well as the most identifiable cancer therapy related cardiac disease. Various definitions are used to define cardiotoxicity related LV dysfunction. American Society of Echocardiography defines LVEF less than 53% or a reduction of 10% to define cardiotoxicity whereas ESMO has set a limit of 50%, at which point cardio protection must be initiated.

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Echocardiography and Cancer Therapy (3/4)

American Society of Echocardiography and European Association of Cardiovascular Imaging have further classified cardiotoxicity into Type I and Type II – difference among these two are highlighted in the Table below.

	Type I	**Type II**
Anti-cancer chemotherapy agents	Doxorubicin	Trastuzumab
Clinical manifestation	New onset of heart failure and LV systolic dysfunction	Asymptomatic decrease in LVEF and less often clinical heart failure
Dose effects	Cumulative, dose dependent	Not dose related
Clinical course	May stabilise with heart failure therapy (ACE inhibitors and beta-blockers), but underlying myocyte destruction appears to be permanent and irreversible	Often reversible with treatment discontinuation (to or near baseline cardiac status in 2–4 months)
Effect of rechallenge	High probability of recurrent dysfunction that is progressive	Rechallenge is often tolerated after recovery

Echocardiography in Calculation of LV Ejection Fraction

Role and Performance

LV EF assessment is done at baseline and thereafter at regular intervals – depending on the drug and dose being administered or as and when symptoms arise.

Calculation of LVEF should be performed using the best method available as per the skills of the operator and the equipment available. Importantly, the same method should be used during subsequent evaluations to define LVEF. Additionally, if possible, digital images should be stored for ease of comparison. According to joint recommendations of ASE / EACVI, modified biplane Simpson's technique with and LV ejection fraction of less than 55% to define LV dysfunction is the recommended modality for calculation of LVEF.

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Echocardiography and Cancer Therapy (4/4)

Limitations as the only criteria for LV function

Although LV function as assessed by LVEF is an easy, objective and reproducible method to define LV function, it suffers from several limitations – a few of these are listed below:

1. Inability to assess small changes in LV function.
2. Dependence on loading conditions of the heart with changes in both pre and after load resulting in a change in measured LV ejection fraction.
3. Inter-observer variability.
4. Reliance on overall LV contractility and non-evaluation of individual segments of left ventricle to assess LV function. To avoid this, ASE recommends a calculation of 16 segment wall motion score for patients on cancer therapy.
5. Poor echocardiography window in post radiotherapy patients.

To conclude, cancer treatment related cardiotoxicity is common. While myocardial dysfunction as assessed by a reduction in the LVEF remains the most widely used and requested parameter for assessment of LV dysfunction, it suffers from several limitations.
Part 2 of the article will define the role of advance echocardiographic tools which help us in early diagnosis and management of cardiotoxicity. It will also elucidate the role of echocardiography in other types of cardiotoxicities such as valvular, coronary and pericardial disease

A Dose of Laughter

1. What happened to the cardiologist who failed his exam?
He had a heart failure.

2. Why did the heart bang so many times for permission?
It had palpitations.

3. Why was the ghost so scared of coming out in the light?
He did not have the heart to do it.

4. What's the heart's favourite shade of red?
Beat-red

5. What happened when the patient refused to get a heart transplant?
He had a change of heart.

6. What did the drum say to the drumstick?
My heart beats for u.

7. Which is the most loving vegetable?
Artichoke, as it has a heart.

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"Cardio-Oncology establishing itself as a new subspecialty in Cardiology" (1/7)

Compiled by Dr Arjun K Ghosh
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Cardio-Oncology is the care of cancer patients with cardiovascular disease. While it has been established a speciality for a few years in the USA and in some parts of Europe, it is now rapidly developing in the UK. This review aims to give the reader of an overview of the exciting new specialty of Cardio-Oncology.

What is Cardio-Oncology?

Cardio-Oncology is the prevention and management of heart disease in cancer patients. While the bulk of work is related to cardiovascular toxicity of cancer therapies it is important to remember that there are other interactions between cancer and heart disease with many common risk factors and disease pathways at cell and molecular level[3].

The mortality rate among patients with cancer has decreased dramatically over the last 20 to 30 years. However, the toxicity of conventional cancer treatment (both chemotherapy and radiotherapy) is greater than previously appreciated and is a leading cause of morbidity and mortality in survivors. New "targeted therapies" are being developed at a rapid pace many of which have recognised or unrecognised cardiovascular toxicities. The cardiac toxicities of cancer treatment include heart failure, cardiac ischaemia, arrhythmias, pericarditis, valve disease and fibrosis of the pericardium and myocardium (Figure 1).

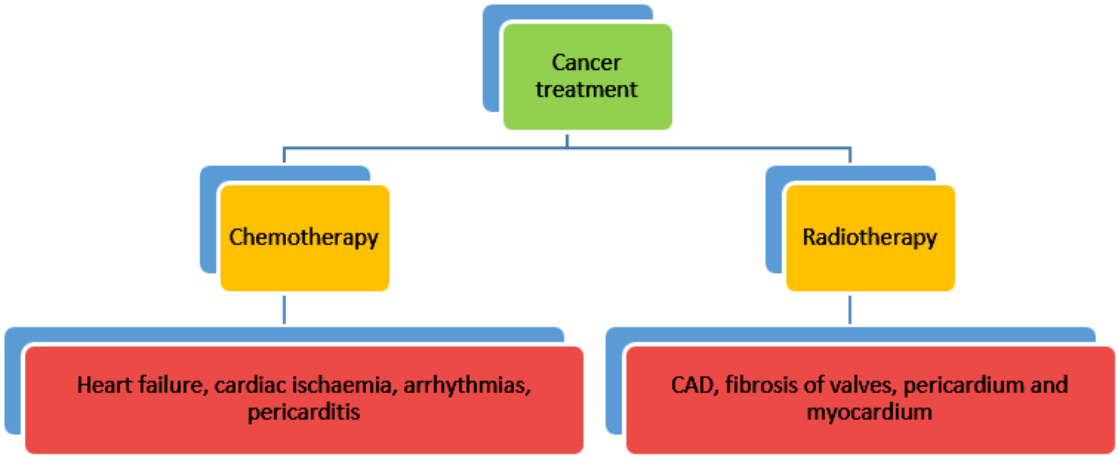

Figure 1. Cardiovascular side effects of cancer treatment

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"Cardio-Oncology establishing itself as a new subspecialty in Cardiology" (2/7)

Chemotherapeutic agents can broadly be divided into cytotoxic agents (anthracyclines e.g., Doxorubicin, taxanes e.g., Paclitaxel and others like 5 Fluorouracil, Cyclophosphamide and Cisplatin) and molecular targeted therapy [Monoclonal antibodies e.g., Trastuzumab (Herceptin), tyrosine kinase inhibitors e.g., Sunitinib and Vascular endothelial growth factor antibodies (VEGFs) e.g., Bevacizumab] (Table 1). The cardiovascular side-effects of these agents are varied (Figure 2). Newer immunotherapies like Chimeric Antigen Receptor T Cell (CART) therapy have their associated cardiotoxicities.

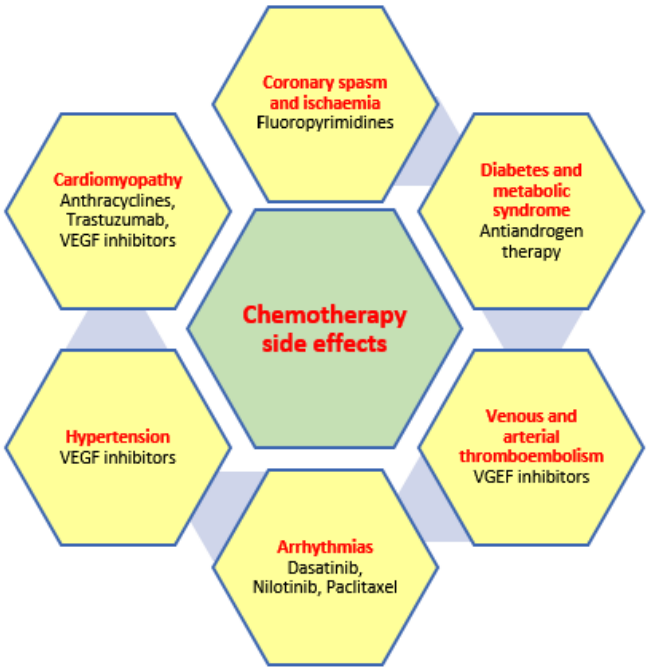

Figure 2. Cardiovascular side effects of chemotherapeutic agents

Radiotherapy can cause cardiac damage through macrovascular and microvascular injury (Figure 3). The risk of radiation-induced heart disease is increased with anterior or left chest irradiation, lack of shielding, higher doses and with concomitant anthracycline chemotherapy[6]. Patients who received radiotherapy historically are at increased risk compared to current radiotherapy regimes due to the development of better shielding protection.

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"Cardio-Oncology establishing itself as a new subspecialty in Cardiology" (3/7)

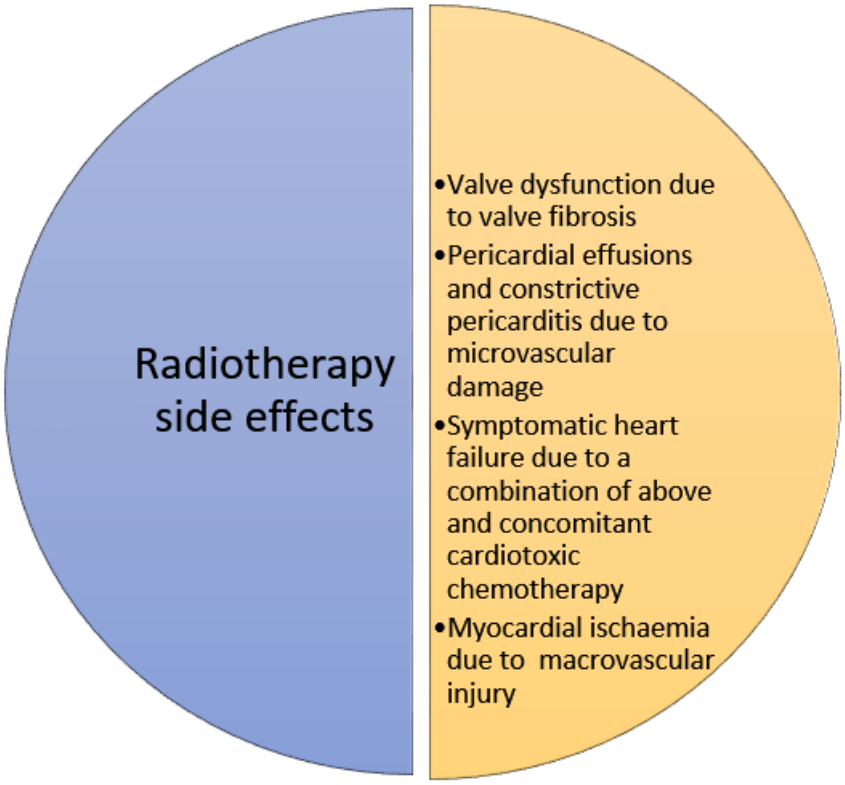

Figure 3. Cardiovascular side effects of cancer radiotherapy

Presentation

Cardio-Oncology patients can present in a number of ways. Depending on the cardiac diagnosis (e.g., heart failure versus ischaemia) different investigations and management plans are formulated.

The key role of Imaging

Cardiac imaging is the primary investigative modality. With the known effect of chemotherapy on cardiac function, cardiac imaging has been used to monitor this. Traditionally in the USA nuclear medicine (MUGA – multi-gated acquisition) scans have been used to monitor ejection fraction (EF) in cancer patients. The predominance of this imaging technique in the USA is due to widespread availability and good reproducibility. However, such an approach has considerable drawbacks – namely repeated exposure to radiation with repeated surveillance scans and an inability to offer a more nuanced assessment of cardiac function other than EF.

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"Cardio-Oncology establishing itself as a new subspecialty in Cardiology" (4/7)

In most other countries, echocardiography is the key initial imaging investigation. It widely available, inexpensive and does not expose the patient to radiation. In the UK the first national guidelines in cardio-oncology were released in March 2021 focusing on the role of echocardiography in monitoring cancer patients[7].

Other imaging modalities have their role also. Cardiac magnetic resonance (CMR) imaging can complement echocardiography by demonstrating the location of focal myocardial fibrosis and inflammation. CMR is however limited by availability, cost and patient acceptance, making it unlikely to wholly supplant echocardiography[8].

Computed Tomography of the Coronary Arteries (CTCA) is also a useful investigation especially when assessing the effects of radiotherapy-induced fibrosis and coronary atherosclerosis[9].

Management and Prevention

Patients with chemotherapy or radiotherapy induced heart failure, valve disease or coronary ischaemia should be treated as per standard European and national guidelines, but some registries suggest that cancer survivors may be undertreated for conventional CV risk factors. The treatment of coronary disease with stents (and the associated antiplatelet agents) may be difficult if cancer surgery or treatment with chemotherapy that may seriously diminish platelet numbers, is imminent.

There is limited data on the cardio-protective effect of Angiotensin Converting Enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and beta blockers in patients undergoing chemotherapy. Their use in this context (e.g., when the EF or strain values drop significantly with chemotherapy but still remain in the "normal" range) is unlicensed. Desraxozane (an iron chelator) has been shown to reduce doxorubicin-induced cardio-toxicity. It may be initiated at the first dose of anthracycline or after a cumulative doxorubicin dosage of ≥ 300 mg/m^2. However, its use is licensed in the treatment of only a few cancers and its use are not widespread and although a previously a worsening in cancer outcomes was suggested, subsequent studies have not confirmed this potential.

The current UK perspective – services and training

There is an increased recognition that optimal cardiovascular care for cancer patients can be best delivered through dedicated Cardio-Oncology services. Cardio-Oncology services are now being developed at a number of hospitals in the UK[2]. Given the increased success of oncological treatments the number of cancer patients with cardiovascular problems will increase with time resulting in a greater need for Cardio-Oncology services. This realization led to the appointment of the first consultant cardiologist in the UK with a special interest in cardio-oncology (the author).

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"Cardio-Oncology establishing itself as a new subspecialty in Cardiology" (5/7)

Training programmes in Cardio-Oncology are well established in the USA with trainees from both Cardiology and Oncology undertaking these fellowships with the ultimate aim of developing Cardio-Oncology services with Cardiologists and Oncologists working together as a team[10]. Currently only a few hospitals in the UK offer Cardio-Oncology Fellowships. The aim of societies like the British Cardio-Oncology Society (http://bc-os.org/), International Cardio-Oncology Society (https://ic-os.org/) and American College of Cardiology (https://www.acc.org/Membership/Sections-and-Councils/Cardio-Oncology) is to expand training in Cardio-Oncology and ultimately develop formal training programmes.

The Asian perspective

Cardio-Oncology is in its infancy in Asia. There is however a growing recognition of cardiotoxicities amongst cardiologists and oncologists leading to the development of the Asian Cardio-Oncology Society and cardio-oncology publications coming from Asian institutions. There is an increasing interest in this area and hopefully the field will continue to grow in the continent.

Key points

- **Cardio-Oncology is a new and exciting specialty involved with the prevention and management of heart disease in cancer patients**
- **Chemotherapy, radiotherapy and cancer itself have cardiovascular effects**
- **Cardiovascular complications include heart failure, valve disease, pericarditis, pericardial effusions, ischaemic heart disease and arrhythmias**
- **Imaging investigations are key for detection of abnormalities and monitoring of patients with echocardiography the principal imaging modality**
- **Limited evidence showing the cardio-protective effect of ACE inhibitors, ARBs and beta blockers – new trials ongoing**
- **Current expansion in Cardio-Oncology services and training opportunities in the UK**

Conflicts of interest

The author is Education lead for the British Cardio-Oncology Society and on the Education Committee of the International Cardio-Oncology Society. He is also on the Cardio-Oncology Leadership Council of the American College of Cardiology.

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"Cardio-Oncology establishing itself as a new subspecialty in Cardiology" (6/7)

Tables
Table 1

Class	Mechanism of action	Typical use
1. Cytotoxic agents		
a. Anthracyclines – Doxorubicin, Daunorubicin, Epirubicin	Intercalate into nuclear DNA, impair topoisomerase II, cell transcription and division, producing Reactive-Oxygen-Species	Leukaemia and soft tissue tumours
b. Taxanes – Paclitaxel, Docetaxel	Polymerise tubulin leading to dysfunctional microtubules disturbing cell division	Breast and ovarian cancer
c. Other agents – 5 Fluorouracil, Capecitabine, Cyclophosphamide, Cisplatin	Bind to DNA causing crosslinking and ultimately apoptosis	Testicular, bladder, ovarian cancer
2. Molecular-targeted therapy		
a. Human epidermal growth factor 2 receptor (HER2) antibody - Trastuzumab	Humanized Immunoglobulin G1 monoclonal Ab directed against the HER2 protein	Breast cancer
b. Tyrosine kinase inhibitors – Lapatinib, Sunitinib, Imatinib	Stop protein activation by blocking signal transduction cascades	Breast, gastrointestinal stromal, renal cancer, leukaemia, non-Hodgkin's Lymphoma
c. Vascular endothelial growth factor (VEGF) inhibitors – Bevacizumab, Sorafenib, Axitinib	Inhibit tumour-associated angiogenesis mediated by VEGF and VEGF receptors.	Brain, kidney, lung, colon cancer
d. Other biologic agents – Rituximab	Monoclonal antibody acting against CD20 protein	Leukaemia, lymphoma

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"Cardio-Oncology establishing itself as a new subspecialty in Cardiology" (7/7)

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Caring for the older cancer patient (1/2)

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Introduction

Older adults are the fastest-growing segment of the population. Population above 65 years of age comprises approximately 5% of the total population of our country (urban 4.8% and rural 5.1%). (1) We are in rapidly ageing world. The incidence of cancers continues to increase in older adults. There is genuine requirement for focussed planning and implementation of optimized care (2). The challenges we face in treating older adults with cancer is enormous.

The various challenges unique to these group include functional decline, fall in physiological reserve, multi-morbidities, geriatric syndromes, psychosocial issues, age bias and lack of evidence base.

The goals of treatment might vary from cure, prolonging survival, symptom control, to “do no harm” and maintain a quality of life. (3) The barriers to diagnosis in older adults are age, ageism, assumptions regarding tolerance to therapy, reduced access to screening, misconceptions regarding etiology, delay in diagnosis and life expectancy being underestimated (4).

Collaboration between a Geriatrician and Oncologist

Assessment of an older cancer patient by a geriatrician helps in assessing vulnerability to cancer treatment, to develop a coordinated plan with the oncologist and in managing geriatric syndromes which can affect the treatment of the cancer. It is important to manage the various non cancer aspects of older adults as they might affect the cancer outcome and also help better cancer care.

A geriatrician can contribute in caring for an older adult with cancer for the following:

-Cognitive problems like dementia, issues with decision making capacity

-functional issues like fall evaluation and prevention, promoting independent living

- multimorbity

-Polypharmacy

-while considering for chemotherapy, radiation therapy and complex surgeries

-Presence of geriatric syndromes

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Caring for the older cancer patient (2/2)

Assessment of Older adults with Cancer

In a study 98% of the Indian geriatric oncology patients had vulnerabilities in at least one geriatric domain emphasizing the need of geriatric assessment. (5) Every older adult is very heterogeneous. They must be assessed in an organised way. A good geriatric assessment should include an assessment of various domains like comorbidities, functional status, depression, mental status, polypharmacy, nutritional status, social support, and living situation

Geriatric assessment may help to identify and address some of the common, age-associated conditions occurring in the older adults**.** Addressing geriatric syndromes or impairments identified could have a significant impact on outcomes such as completion of chemotherapy, morbidity or mortality, quality of life, as well as on the number of emergency department visits and hospitalization rates. (6)

The best step forward would be:

- The development of shared care protocol by Geriatricians and Oncologists
- Awareness and training programs for early detection of common cancers in the older population in different healthcare settings
- Multi-disciplinary care teams
- Focus on Quality of life and patient reported outcomes
- Focus on survivorship issues
- Focus on caregiver stress

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Radiation induced cardiac toxicity (1/5)

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It is estimated that more than 60 % patients need radiation during their lifetime for treatment of cancer. It may be administered as primary modality of treatment, before or after surgery or chemotherapy or along with chemotherapy and also in palliative setting. Radiation-induced heart disease (RIHD) is a term used to describe all cardiac complications related to RT. Pericardial disease, ischemic heart disease, non-ischemic cardiomyopathy, valvular disease, conduction abnormalities, and arrhythmias have all been independently linked to chest radiation. (1,2) Pericardial abnormalities are most common and conduction abnormalities are rarely seen. It generally occurs after a latent period of 10-15 years and so it's very paramount to keep a watch on younger patients.

Radiation is most commonly delivered as a local/regional treatment by an external beam consisting of photons, electrons, protons, or heavy particles but may also be delivered via brachytherapy (where a sealed radiation source is placed adjacent to the target) or systemically via unsealed sources.

In general, thoracic RT that exceeds 30 Gy is considered a high dose that leads to high mean cardiac dose and places patients at increased risk for RIHD [4, 13]. In a retrospective study of 2,232 patients with Hodgkin's lymphoma who received RT, it was found that total doses of >30 Gy resulted in a 3.5-fold higher risk for cardiac death compared to a matched general population. (3)

Mean heart doses of 20 Gy were associated with 2-year risk adjusted cardiac event rates of 4, 7, and 21%, respectively. (4) In addition, LV volume receiving >5 Gy was significantly associated with cardiac events including symptomatic pericardial effusion, pericarditis, myocardial infarction, unstable angina, and heart failure. (4) In a retrospective cohort of 2,524 Dutch patients treated for Hodgkin's lymphoma, it was found that patients younger than 25 years had a 4.6- to 7.5-fold increased risk of CAD [5]

Radiation related factors

RIHD depends on a number of patient and treatment related factors. These are listed below.

1. Total dose of radiation
2. Beam energy
3. Type of radiation used (photons, electrons, protons)
4. Technique of radiation – Tangential,3DCRT, IMRT, DIBH, Prone position, Pericardial block, subcarinal block
5. Dose per fraction> 3 Gy more pericardial effusion

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6. Volume of heart irradiated
7. Volume of heart muscle exposed
8. Mean heart dose
9. Proximity of heart to tissue radiated
10. Left sided vs right sided breast radiated, RT of left sided thorax
11. Internal mammary radiation

Patient related factors

1. Early age at radiation
2. Smoking- 3 times more risk
3. Hyperlipidaemia
4. DM
5. Hypertension
6. Obesity
7. Pre-existing cardiac ds
8. Adjuvant treatment with cardiotoxic chemotherapy
9. Concurrent treatment with trastuzumab or anthracyclines
10. Genetic susceptibility- mutation in DNA repair pathways
11. Life style habits

Clinical manifestations and diagnosis

The radiation to heart can cause acute or chronic side effects. A good history taking, thorough clinical examination, awareness of side effects of radiation and high index of suspicion are a must for any Cardiologist who looks after cancer patients. The signs, symptoms and treatment depend on dose received to each part of heart.

Part involved	Symptoms	Acute effects	Chronic effects	RT Dose	Intervention
Pericardium	Fever Chest pain Pericardial pain Dyspnea Low BP, weak pulse Elevated JVP	Pericarditis Pericardial effusion May be self-limiting	Usually after 1yr Pericardial fibrosis Restrictive pericarditis Diastolic dysfunction Cardiac tamponade	>35 Gy	Monitor closely NSAIDS Diuretics Loop diuretics Pericardial window Pericardiectomy

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Valvular heart ds	Symptoms and signs of heart failure	In addition to valves, surrounding structures including the annulus of the valve, sub valvular apparatus, and aorto-mitral curtain are involved	Fibrosis Thickening Calcification Mainly left sided valves Stenosis Regurgitation May lead to endocarditis	>30 Gy MC aortic regurgitation	Depending on location of valve Dilatation and valvopathy Transcatheter intervention
Myocardium	Dyspnoea Fatigue Edema Orthopnea Paroxysmal nocturnal dyspnea Exercise intolerance	Increases after 5yrs	Diffuse fibrosis Restrictive myocarditis Systolic heart failure Cardiomyocyte toxicity Non ischemic cardiomyopathy	>30Gy More if combined with anthracyclines and Trastuzumab	Could be multifactorial so identify the cause Lop diuretics ACE inhibitors Nitroglycerines Vasodilators Ionotropes
SA and AV nodes Conduction abnormalities	Light-headedness Syncope Palpitation Chest discomfort Aortic and mitral valves MC	Asymptomatic ds 11.5 yrs, symptomatic 16.5 yrs	1-23 yrs after RT Arrythmias Damage to cardiac nodes Bundle branch block	MC abnormality are infranodal and RBBB	Antiplatelets Antiarrythmics Pacemaker Catheter ablation Also provide prophylaxis for endocarditis
CAD	Acute angina, Acute coronary syndrome Ischemic cardiomyopathy Heart failure	Inflammatory effects of RT worsen atherosclerosis	Unstable angina MI Cardiac mortality Coronary lesions are mainly located in the ostia or the proximal portions of the epicardial vessels LAD, rt CA, ant part of heart more affected	As low as 6 Gy MHD > 4 Gy 7.4% increase risk with each 1 Gy mean heart dose	Risk starts to increase at 5 yrs and up to 20 yrs so long-term monitoring Antiplatelets ACE-, Beta blockers Dilatation Stents Bypass graft IMA may not be available for graft if recd. RT
Carotid a.	TIA Stroke		Extensive fibrosis	Long segment involved	Carotid stenting
Autonomic dysfunction	Blunted blood pressure or heart response to exercise				

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Options to prevent heart toxicity

1. Limit RT dose to LAD and MHD- for every 1 cm increase in MHD, mean heart dose increased by 2.9%. Keep MHD less than 1 cm. Quantec recommends to keep the mean heart dose <26 Gy to keep the risk of pericarditis <15%. Also keep V30<45% to keep pericarditis < 15%. Contour coronary arteries and document the dose and limit the dose to minimum. (6)
2. Usage of IMRT
3. Prone position
4. DIBH- Deep inspiratory breath hold
5. Heavy ions, protons
6. Identify and correct predisposing factors as DM, HTN, Hyperlipidaemia
7. Smoking cessation counselling
8. Full cardiac evaluation with ECG, Echocardiography before anthracyclines, trastuzumab
9. Judicious and proper use of cardio-toxic drugs
10. Lifestyle modifications

Now with better radiation techniques average mean heart dose for left sided breast cancer has been reduced from 5.1 to 3 Gy. Also, over the years from 1970 to 2006, there has been a decrease in mean dose to heart and coronary vessels from 13.3 to 3.3 Gy from heart and 31.8 Gy to 7.6 Gy for LAD. (6). It's important to note that radio-biologically heart is both a serial and parallel organ. (3)

In the SAVE-HEART study, in 89 patients with left-sided breast cancer, the use of deep inspiration breath-hold reduced mean heart radiation doses by 35% (interquartile range: 23–46%) as compared to free breathing, which translated to a greater reduction in expected years of life lost due to RIHD (0.07 vs. 0.11 years, respectively) [7]. In another study, intensity-modulated RT and moderate deep inspiration breath-hold significantly reduced heart V30 from 19.1 to 3.1% ($p < 0.0004$) [8]. In a more recent study of 49 patients with left-sided breast cancer, a multi-leaf collimator modification technique was tested and resulted in significant reduction in the mean left anterior descending artery (LAD) dose by 7.0 Gy, the mean LAD planning risk volume dose by 5.9 Gy, the maximum LAD dose by 12 Gy, and the mean heart dose by 0.73 Gy, whilst maintaining breast and boost volume dosimetry (9).

Early detection of cardiac abnormalities

A number of tests are being done for early detection of cardiac abnormalities.

1. Troponin -not been validated in predicting the development of RIHD
2. Brain natriuretic peptide- not been validated in predicting the development of RIHD
3. Placental growth factor and growth differentiation factor 15- need further studies
4. Screening echocardiography - can tell us about association of mean and maximum LV dose and a decrease in LVEF (57.6–56.4%) as well as worsening global longitudinal myocardial strain
5. Coronary calcium score (CAC) - can detect preclinical coronary atherosclerosis, but not other parameters
6. SPECT- 40% patients may have perfusion defects after RT
7. Development of fluid between the epicardium and pericardium is one of the salient features of RIHD.

Current recommendation is for screening echocardiogram 5 years after chest radiation in high-risk patients and 10 years in the other patients [69]. Functional non-invasive stress test is recommended 5–10 years after chest radiation in high-risk patients

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Radiation induced cardiac toxicity (5/5)

Secondary prevention

1. Metformin –some studies speak in favour of this
2. Aspirin, statin, and colchicine- more work needed

Treatment of RIHD

Independent predictors of mortality are balloon angioplasty, bare-metal stent placement, SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score of ≥11, New York Heart Association functional class ≥3, history of smoking and age ≥65 years [Modern, ref 49).

The risk of cardiac mortality is more in patients with RT induced cardiac toxicity vs non-RT induced cardiac diseases. In addition, they are at increased risk of pre-existing valvular and conduction abnormalities so it's crucial to plan revascularisation procedures in radiated patients very carefully. The best treatment strategy would be to recognise the problem, identify predisposing factors, use preventive strategies and take timely and appropriate action for the accompaniments of radiation.

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Black box warning with anthracyclines (1/2)

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What is black box warning? Also called as "Boxed warning", black box warning is a mandate required by US FDA for certain drugs with potential rare but serious/fatal side effects. They are supposed to be printed in bold font surrounded by black thick margins appearing as box and has to appear in front as soon as one opens package insert of the drug.

First implemented in 1979, it is estimated that over 600 medications carry black box warning. Evidence to implement black box mostly comes from observation rather than clinical trials. Black box warning typically informs physicians about fatal side effects of the drug, how to prevent them and to avoid usage in which special population.

Anthracyclines (Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Mitoxanterone and Valrubicin) are antineoplastic drugs, commonly called as Topoisomerase II inhibitors and are derived from streptomycin species. FDA approved indication for anthracyclines is present in 14 different cancers. Since the first report of daunorubicin causing congestive heart failure in 1966 by Karnofsky from USA, there are many papers publishing the same. As a result, anthracycline class, in general, carries a black box warning about cardiotoxicity. Doxorubicin, an anthracycline, in fact carries 4 black box warnings: severe cardiomyopathy, second malignancies, drug extravasation leading to tissue necrosis and severe myelosuppression.

Three sets of information are required in black box warning as per format mandated by US FDA.

Fatality and incidence of the side effect:

The probability of developing cardiomyopathy is generally directly proportional to the cumulative dose of the drug.

Total cumulative dose of doxorubicin - 300 mg/m2- 1-2%
400 mg/m2- 3-5%
450 mg/m2- 5-8%
500 mg/m2- 6-20%

This is seen when doxorubicin is administered every 3 weeks.

There is an additive or potentially synergistic increase in the risk of cardiomyopathy in patients who have received radiotherapy to the mediastinum or concomitant therapy with other known cardiotoxic agents such as cyclophosphamide and Trastuzumab.

How to avoid this side effect?

1) Assess left ventricular cardiac function (e.g., MUGA or echocardiogram) prior to initiation of doxorubicin, during treatment to detect acute changes, and after treatment to detect delayed cardiotoxicity.
2) Increase the frequency of assessments as the cumulative dose exceeds 300 mg/m2.
3) Use the same method of assessment of LVEF at all time points

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Black box warning with anthracyclines (2/2)

4) Consider the use of dexrazoxane to reduce the incidence and severity of cardiomyopathy due to doxorubicin administration in patients who have received a cumulative doxorubicin dose of 300 mg/m2 and who will continue to receive doxorubicin.

Contraindications to administer anthracyclines

- Severe myocardial insufficiency
- Recent history of myocardial infarction (i.e., occurring within the past 4 to 6 weeks)

Healthy Heart Quotes - Make your health your priority.

1. Most people have no idea how good their body is designed to feel.
2. Listen to your heart. It may be on your left but it's always right.
3. The problem with heart disease is first symptoms may be fatal.
4. Don't lose heart- Loose cigarettes, lose junk food, loosen up and move.
5. Beat the heart disease and feel the healthy beat.
6. Self-care is not self-indulgence. It's self-preservation.
7. Being healthy and fit is not a fad or a trend, it's a lifestyle.
8. Exercise should be regarded as a tribute to the heart.
9. Physical fitness is not only one of the most important keys to a healthy body. It's the basis of a dynamic and creative intellectual activity.
10. The body loves routine. Try to eat, sleep and so on at the same times every day in order for the body to function at its optimum capacity. The body loves consistency.
11. Exercise is king. Nutrition is queen. Put them together to create your own kingdom.
12. Today more than 95% of chronic diseases are caused by food choice, toxic food ingredients, nutritional deficiencies, and lack of physical exercise.
13. 30% exercise, 70% healthy eating.
14. A 1-hour workout is 4% of your day. NO EXCUSES.
15. You are only 1 workout away from good mood.
16. When it comes to eating right and exercising, there is no" I'll start tomorrow". Tomorrow is a disease.
17. When you cut out sugar, you will be cutting out a boatload of empty, useless calories which will help weight loss. Rest a while and run a mile.
18. What you eat literally becomes you. You have a choice in what you are made off.
19. Exercise is a celebration of what you can do and not a punishment for what you ate.
20. The difference between "try" and "triumph' is just a little" umph".
21. There is no better exercise for strengthening the heart than reaching down and lifting another up.
22. The real purpose of running is not to win a race but to test the limits of the human heart.
23. Think positively and exercise daily, eat healthy, work hard, stay strong, build faith, worry less, read more, be happy, relax, love, live.
24. We wish that your heart always stays healthy and happy so take care of your diet and always keep your heart in good shape.
25. Did you work out today?

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