



Review Article

Cardio-Oncology – A new subspecialty with collaboration at its heart

Arjun K. Ghosh^{a,*}, J. Malcolm Walker^b^a Barts Heart Centre, St Bartholomew's Hospital and Hatter Cardiovascular Institute, University College London Hospital, United Kingdom^b Hatter Cardiovascular Institute, University College London Hospital, United Kingdom

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ABSTRACT

Cardio-Oncology is the care of cancer patients with cardiovascular disease, overt or occult, already established or acquired during treatment. Cancer patients can present with a variety of cardiovascular problems not all of which are directly related to cancer therapy (medications or radiotherapy). The cardiovascular problems of oncology patients can range from ischaemia to arrhythmias and can also include valve problems and heart failure. As such, within cardiology, teamwork is required with members of different cardiology subspecialties. The way forward will be to adopt a multidisciplinary approach to produce optimal individual care. Close collaboration between cardiology and oncology specialists in a Cardio-Oncology setting can make this happen.

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Cardio-Oncology is the care of cancer patients with cardiovascular disease, overt or occult, already established or acquired during treatment also includes the prevention, early recognition, and mitigation of the effects of modern cancer treatment on the cardiovascular system.

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.¹ New “targeted therapies” are being developed at a rapid pace many of which have recognized or unrecognized cardiovascular toxicities.

Although Cardio-Oncology is often regarded as synonymous with treating the 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.² The cardiac toxicities of cancer treatment include heart failure, cardiac ischaemia, arrhythmias, pericarditis, valve disease and fibrosis of the pericardium and myocardium.³

While Cardio-Oncology services have been established in the USA and in parts of Europe it is still a relatively new concept in the UK and many other countries. Nevertheless, a perceived clinical need is driving a number of hospitals to develop formal Cardio-Oncology services such as at the Barts Heart Centre, St Bartholomew's Hospital London and University College London Hospital⁴ and this is also reflected in a number of recent Cardio-Oncology guidelines.^{5,6}

Cancer patients can present with a variety of cardiovascular problems not all of which are directly related to cancer therapy

* Corresponding author at: Department of Cardiology, Barts Heart Centre, St Bartholomew's Hospital, London EC1A 7BE, United Kingdom.

E-mail address: arjun.ghosh@bartshealth.nhs.uk (A.K. Ghosh).

(medications or radiotherapy). Optimal individual care requires close collaboration between cardiology and oncology specialists.

1. Arrhythmias and device issues – collaborating with the Electrophysiology (EP) team

Arrhythmias are frequently associated with treatment in cancer patients.^{7,8} The commonest unsurprisingly is atrial fibrillation (AF),^{9,10} but supraventricular tachycardias and repolarization issues, particularly QT prolongation and torsades de pointes (TdP) are also encountered.¹¹

Multiple studies have demonstrated an increased association between AF and malignancies and chemotherapy, even accounting for conventional AF risk factors.⁹ The mechanisms¹² by which chemotherapeutic agents can cause AF vary and are outside the scope of this article. However, the treatment on AF in cancer patients is challenging as many rhythm-controlling agents interact with cancer therapies and even though these patients may have an increased propensity to stroke, anticoagulation can also be problematic, due to anaemia and low platelet counts which are prevalent in this population. Ablation is of course an option in these patients although here, as in most other areas of Cardio-Oncology, there is a dearth of high-quality (i.e. Class 1 Level A) evidence.¹³

Many cancer drugs prolong the QT interval. In addition, a number of co-existing factors in cancer patients can affect the QT interval (Fig. 1). This can lead to potentially fatal TdP.

The measurement and monitoring of the QT interval can be difficult with one study showing disagreement amongst 75% of Cardiologists and 38% of electrophysiologists when assessing the QT interval.¹⁴ While the Bazett formula ($QT_c = QT/\sqrt{RR}$ where RR is RR interval in seconds) is most widely used in clinical practice the Fridericia formula ($QT_c = QT/RR^{1/3}$) may be more appropriate in the Cardio-Oncology population as it is more accurate at slower heart rates and does not significantly over-correct at faster heart rates.¹⁵ Another problem with QT monitoring in cancer patients is that while the QT interval is often prolonged at baseline due to a variety of reasons this may not always translate into a significant arrhythmia risk.¹⁶

There has been a dramatic increase in the utilization of implantable cardiac rhythm devices e.g. pacemakers, implantable

cardiac defibrillators (ICDs) and cardiac resynchronization therapy (CRT) devices over the last few decades.¹⁷ This cohort of patients pose particular difficulties when undergoing cancer therapy (particularly thoracic radiotherapy) and may require careful re-programming or occasionally explantation prior to localized radiotherapy.¹⁸ With increasing life-expectancy more patients are being seen with both cancer and an implantable cardiac device. Radiotherapy in the region of the device may lead to increased sensor rate, change in pacing rate or thresholds, rarely battery depletion or permanent device malfunction. Different device companies have published their own recommendations for management of an implantable cardiac device in the event of radiotherapy. These should be followed along with local and international guidance.^{19,20} In general direct radiation of the device should be avoided. In rare cases the device may have to be removed and re-implanted at the same or contralateral side after completion of therapy.

2. Heart failure – collaboration with the multidisciplinary heart failure team

While new treatment options have dramatically decreased cancer mortality in recent years, a number of these chemotherapeutic agents are cardiotoxic.²¹ Anthracyclines (Doxorubicin, Daunorubicin, and Epirubicin), alkylating agents (Cyclophosphamide), monoclonal antibodies (Trastuzumab) and tyrosine kinase inhibitors have all been implicated in causing left ventricular dysfunction. Higher cumulative doses of anthracyclines are associated with a greater chance of developing heart failure.²² It is felt that anthracycline mediated cardiotoxicity is permanent, the so-called type 1 cardiotoxicity; explained by the production of ultrastructural myocyte damage. Non-anthracycline cardiotoxicity, classically seen with Trastuzumab (Herceptin) may be reversible and has been called type 2 cardiotoxicity.² However, it should be borne in mind that functional improvement may occur in anthracycline-related cardiotoxicity through the use of appropriate cardiac therapy (e.g. heart failure medications) and that cardiac dysfunction associated with Trastuzumab may not necessarily recover despite appropriate therapy.²³ This may indicate that additional undiscovered factors have a role in the mechanism and extent of cardiotoxicity caused by these agents.²⁴ Cytotoxic

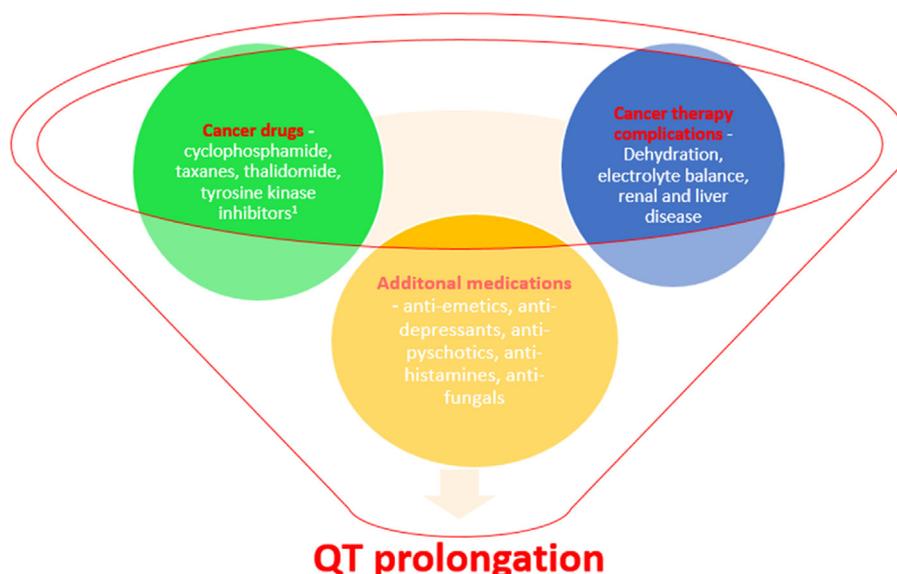


Fig. 1. Multifactorial causes for QT prolongation in cancer patients.¹ Cancer drugs can increase the QT interval via primary electrophysiological effects, or via secondary effects, such as ischaemia or heart failure.

cardiac dysfunction (CCD) can be acute, early (within 1 year) or late. Acute and early cardiac dysfunction may often recover while late presenters often have a worse clinical course.²⁵ The presence of other cardiac risk factors e.g. diabetes and coronary artery disease can increase the incidence of heart failure in this population group.²⁶ Combination therapy with anthracyclines and Trastuzumab doubles the risk of developing heart failure compared to anthracycline therapy alone (5.2% versus 2.5% at 5 years), however when the interval between the administration of these drugs is greater than three months, there is almost no increased toxicity.²⁷

A number of studies have investigated the role of treatments to prevent cardiotoxicity and biomarkers or imaging to detect pre-clinical injury (see below). Dexamethasone, Angiotensin Converting Enzyme (ACE) inhibitors, beta blockers and statins have been postulated to have protective roles.²⁸ The PRADA (Prevention of cArdiac Dysfunction during Adjuvant breast cancer therapy) trial published this year is the largest randomized control trial to date looking at the prevention of cardiac dysfunction in a breast cancer population and is a much-needed and welcome addition to the Cardio-Oncology evidence base.²⁹ PRADA was a double-blinded, placebo-controlled 2 × 2 factorial design, single-centre trial. 120 patients with early breast cancer were recruited. Study members were randomized to candesartan 8 mg a day (target dose 32 mg a day) or metoprolol 25 mg a day (target dose 100 mg a day) or placebo after breast cancer surgery but before the initiation of anthracycline-containing chemotherapy.³⁰

The primary endpoint was change in LVEF measured by Cardiac magnetic resonance (CMR) scanning from baseline to the completion of adjuvant therapy. Therapy was completed after 10 to 64 weeks depending upon the combination of

chemotherapeutic agents used and the need for radiotherapy. LVEF declined by 0.8% in the candesartan group, 1.6% in the metoprolol group and 2.6% in the placebo group. The change in LVEF in the candesartan group was statistically significant compared to placebo ($p=0.026$).

Somewhat surprisingly no differences were seen between candesartan and placebo when global longitudinal strain (GLS, a subtler marker of LV function), diastolic function and cardiac biomarkers [troponin and brain natriuretic peptide (BNP)] were compared. While Metoprolol did not provide statistically significant protection against LVEF decline it was associated with a significant improvement in diastolic function as measured by E/e' (an increase in 0.8; p value = 0.009).

It should however be emphasized that while the PRADA trial has provided helpful data, it is a small trial and meta-analyses have shown the benefit of beta-blockers in Cardio-Oncology patients.²⁸

It is important to remember that radiotherapy in cancer patients can cause wide-ranging cardiac damage including heart failure.^{31–33} Radio-therapy-induced cardiac damage was more common earlier but modern techniques such as focussed beam radiotherapy and better shielding have decreased the prevalence.³⁴ However, nature (location, strength, duration) previous radiotherapy remains a very important component of the “past medical history” to elicit when assessing any Cardio-Oncology patient (and for many cardiology patients where it is missed). Macro and microvascular injury can accelerate age-related atherosclerosis which may lead to myocardial infarction or focal fibrosis and associated abnormalities in systolic and diastolic function. In addition, radiotherapy can cause pericardial inflammation and ultimately constrictive pericarditis.³⁵ Radiotherapy can also cause endothelial injury in cardiac valves leading to



Fig. 2. Factors to be considered when deciding on intervention to prevent cardiotoxicity. GLS – global longitudinal strain, EF – ejection fraction.

regurgitation and/or stenosis which may precipitate heart failure.³⁶

Once heart failure has been diagnosed patients should be treated following established heart failure guidelines.^{37,38} However those cancer patients with asymptomatic documented falls in LVEF or global longitudinal strain, but whose parameters remain within the “normal” ranges (see below) pose particular difficulties. Should cancer therapy be adjusted, changed or abandoned and should heart failure medication be introduced (Fig. 2)?

The role of biomarkers in this context has been explored but controversy still exists.^{39–41} The exact timing of blood tests (e.g. Troponin and N-Terminal Brain Natriuretic Peptide) to detect cardiotoxicity at an early stage is currently under investigation as is their precise role in guiding therapy. Nevertheless, clinicians find these measures useful in individual cases and there is data to suggest early cardiac intervention, where biomarkers are elevated, may improve outcomes (at least where LVEF is concerned).^{42,43}

Cancer patients with established heart failure should be managed closely with the heart failure team to allow seamless integration into community heart failure services. Working closely with heart failure services also facilitates palliative care input from a heart failure perspective given that a proportion of these patients die of heart failure and/or cardiovascular complications after their cancer is cured.⁴⁴

Ultimately as with other heart failure patients (and with patients in general)⁴⁵ a personalized approach is needed. Changes to cancer therapy cannot be made purely based on numerical changes in biomarkers or imaging parameters. Cancer prognosis/spread of disease and response to cancer therapy are key considerations in deciding when and how aggressively to intervene from a cardiac perspective. In the authors' opinion, the aim of a Cardio-Oncology service should be support cancer patients in completing their cancer therapy as far as practical rather than causing it to be suspended prematurely before completion.⁴⁶

3. Integrating cardiovascular imaging in the care of Cardio-Oncology patients

Cardiac imaging is integral to the management of Cardio-Oncology patients. Imaging has a role in screening, early detection of cardiotoxicity and in assessment of response to cardioprotective therapy.⁴⁶

There is a long and established history of nuclear medicine (MUGA – multi-gated acquisition) scans to assess LVEF in cardiac patients.⁴⁷ This technique has also been used to monitor LVEF in cancer patients in many centres.^{48,49} While this technique is reproducible it has drawbacks – including repeated exposure to

radiation with surveillance scans and an inability to offer a complete assessment of cardiac function other than a single parameter of systolic performance, the LVEF (Table 1).

Currently in most countries echocardiography is the key initial imaging investigation. It is widely available and does not expose the patient to radiation. In addition, it can evaluate systolic and diastolic function in addition to valve disease and pericardial effusions. Echocardiography has also been used primarily for surveillance of those undergoing cardio-toxic treatment. Older guidelines focussed on repeated monitoring of LVEF with a decrease in EF below a certain level often driving the postponement or interruption of cancer treatment.³⁷

Changes in LVEF are late markers in the assessment of cardiac function when compared to changes in newer markers such as global longitudinal strain.^{50–52} LVEF is a composite marker reflecting longitudinal, radial and circumferential myocardial contractility. A deterioration in any one of these types of contractility can be compensated for by increased contractility in the other two directions. As such the LVEF may remain unchanged despite deterioration in one aspect of contractility and is thus an insensitive marker of myocardial function.⁵³ In addition, the recommendations regarding the level of change in serial LVEF measurements that mandate alterations in chemotherapeutic approach, are close to the coefficient of variability for LVEF, assessed by routine departmental echocardiography.³⁷

The use of 3D echocardiographic to obtain volumetric LVEF calculations is more reproducible, compares favourably with cardiac magnetic resonance LVEF calculations and is advocated as the preferred echocardiographic method of calculating LVEF.⁵⁴

Newer parameters of deformation and contractility hold the prospect of being able to identify cardiac involvement before LVEF changes, and thus alert clinicians early, before irreversible damage occurs. Candidate parameters include echocardiographic strain imaging, tissue Doppler annular velocities and chamber volumes. Current guidelines recommend strain imaging in monitoring for cardio-toxicity.³¹

Echocardiography can, in addition, help elicit other complications of cancer therapy e.g. pericardial effusions, pericardial constriction and valve degeneration.⁵⁴ Stress echocardiography (or any other form of functional cardiac imaging) can also determine if there is significant radiotherapy-associated accelerate atherosclerotic coronary artery disease.¹³

CMR imaging can complement echocardiography by demonstrating the location of focal myocardial fibrosis by late gadolinium imaging and diffuse fibrosis by the newer T1 and T2 mapping techniques.⁵⁵ CMR can also identify acute inflammatory changes associated with chemotherapy and can be invaluable in monitoring for the resolution of cardiac oedema in this context.⁵⁶ CMR is

Table 1

Comparison of different cardiac imaging modalities used to image oncology patients. GLS – global longitudinal strain, CMR – cardiac magnetic resonance, EF – ejection fraction, CTCA – computed tomography of the coronary arteries.

Imaging modality	Strengths	Drawbacks
Echocardiography	Widely available Ability to measure subtle markers of abnormality e.g. GLS Can assess functional implications of coronary artery disease (stress echocardiography) Full assessment of valve disease and diastolic function	Inter and intra-observer variability (less with 3D echocardiography or with contrast echocardiography) Inability to obtain optimal images in all patients
CMR	Ability to accurately and reproducibly assess EF Can assess functional implications of coronary artery disease (stress CMR) Assessment of cardiac fibrosis (may be related to chemotherapy)	Not as widely available Cost
Nuclear Cardiology	Long-established technique for assessing EF with significant literature-base	Inability to assess subtle markers of cardiac function Inability to assess valve disease or pericardial effusions Radiation dose
CTCA	Anatomical assessment of coronary artery disease	Not as widely available Radiation dose

however limited by availability, cost and patient acceptance, making it unlikely to wholly supplant echocardiography.

Computed Tomography of the Coronary Arteries (CTCA) is also a useful investigation especially when assessing the effects of radiotherapy-induced fibrosis and coronary atherosclerosis and has been recommended in European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines.^{31,54}

Close collaboration with departmental cardiac imaging specialists is required to develop local protocols for the screening of cancer patients and monitoring of individuals on cardio-toxic chemotherapy and radiotherapy, as well as the systems for longer term surveillance of those likely to develop late complications.³

4. Interventional issues

Coronary intervention in Cardio-Oncology patients can be problematic. Anaemia and abnormal platelet numbers and function are commonly seen in cancer patients which can complicate use of antiplatelet agents and drug-eluting balloons and stents.⁵⁷ Approximately 10% of cancer patients have thrombocytopenia (TP) (platelet count $<100,000\text{ mm}^{-3}$).⁵⁸ TP is associated with increased risk of thrombus formation as platelet function is more important than number.

A number of considerations need to be taken into account before coronary intervention is undertaken (Fig. 3).

The general prognosis from the cancer needs to be considered although this itself is a very challenging calculation.⁵⁹ If the consensus opinion is that prognosis is >1 year optimal revascularization should be considered if clinically appropriate. In the setting of an acute coronary syndrome (ACS) revascularisation should be considered. The form this may take (i.e. bare metal stent versus drug eluting stent) will depend on a variety of factors as outlined in Fig. 3. Such decisions should ideally be made in the context of a multidisciplinary team (MDT) setting. While such formal review in an MDT setting may not be possible for all cases, especially in patients presenting acutely, at a minimum, discussion with the on-call oncologist/haematologist should occur. In patients with stable angina medical treatment is the preferred option. If percutaneous intervention (PCI) is considered to achieve symptomatic benefit, Fractional Flow Reserve (FFR) (or non-invasive stress imaging) should be performed to determine necessity of intervention. Coronary artery bypass surgery (CABG) may be considered if the cancer is curable or when the estimated prognosis is acceptable.⁶⁰

Plain old balloon angioplasty (POBA) may be considered an option if the platelet count is $<30,000\text{ mm}^{-3}$ or when a cancer surgery or procedure is imminently required. Bare metal stents may be used if cancer surgery can be delayed by 4 weeks.

- Acute or elective cardiac presentation
- Prognosis (from oncologic and cardiac perspectives)
- Patient symptoms
- Platelet count
- Other comorbidities e.g. renal function, general mobility
- Tolerability of antiplatelet therapy
- Patient/family choice

Fig. 3. Key considerations prior to coronary intervention in cancer patients.

Intravascular ultrasound (IVUS) or Optical Coherence Tomography (OCT) is recommended to ensure optimal stent expansion in case dual anti-platelet therapy (DAPT) needs to be stopped prematurely. The use of absorbable coronary stents is yet to be widely adopted, but may hold promise in this patient group as it may allow decreased duration of concomitant DAPT.

While there is no minimum platelet count required to perform a diagnostic coronary angiogram prophylactic platelet transfusion may be recommended by Oncology/Haematology teams in the following situations⁵⁸:

- (a) Platelet count $<20,000\text{ mm}^{-3}$ and one of the following (i) high fever, (ii) leucocytosis, (iii) rapid drop in platelet levels, (iv) other coagulation abnormality
- (b) Platelet count $<20,000\text{ mm}^{-3}$ in solid tumour patients receiving therapy for bladder, gynaecological or colorectal tumours, melanoma or necrotic tumours

Radial access is preferred in this population group. Ideally all non-emergency cases should be discussed with the referring team in a multi-disciplinary setting. The complexity of such patients again mandates a personalized approach to therapy as discussed previously (in the heart failure section).

The role of radiotherapy in accelerating age-related atherosclerosis should also be borne in mind when assessing patients with chest pain as it may lead to symptomatic coronary artery disease in an atypical population group i.e. in younger females exposed to radiotherapy in childhood.^{32,61}

5. The role of exercise therapy and the cardiac rehabilitation team

Aerobic exercise is associated with partial reversal of detrimental inflammatory effects on vascular endothelium and can reduce overall cardiovascular risk.^{62,63} Cancer can directly cause deleterious effects on vascular tissue while also increasing cardiac risk by limiting overall physical activity leading to weight gain.^{64,65}

Exercise-based interventions can exert multiple beneficial cardio-metabolic effects, lowering blood pressure, modulating the renin-angiotensin system, decreasing abdominal fat and improving insulin sensitivity and lipid profile.⁶⁶ The role of exercise therapies in cancer patients has received increasing attention in recent years with benefits seen in physical function, quality of life and fatigue.⁶⁷ Epidemiologic data have postulated associations between decreased physical activity and cancer recurrence⁶⁸ and worse outcomes.⁶⁹

The beneficial effects of formal exercise therapy in cardiovascular disease and heart failure are established.⁷⁰ Randomized trials have also shown a cardiovascular benefit to exercise training in patients with early-stage cancer.⁷¹ Ideally local cardiac rehabilitation services should consider the needs of cancer patients (without a formal diagnosis of heart failure).⁷² However, for this to become standard guideline-based practice it is likely that the cost-benefit of such an intervention will have to be conclusively determined.

6. Conclusion

Cardio-Oncology is an exciting area of medicine straddling cardiology and oncology which is gaining increased recognition. The optimal management of Cardio-Oncology patients requires knowledge of all Cardiology subspecialties and requires close collaboration with experts in the different subspecialties. A multi-disciplinary approach to these complex patients is likely to produce the best outcomes.⁷³

Conflicts of interest

All submissions must include disclosure of all relationships that could be viewed as presenting a potential conflict of interest.

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