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The role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a Position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC)

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Abstract

Cardiovascular (CV) imaging is an important tool in baseline risk assessment and detection of CV disease in oncology patients receiving cardiotoxic cancer therapies. This position statement examines the role of echocardiography, cardiac magnetic resonance, nuclear

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cardiac imaging and computed tomography in the management of cancer patients. The Imaging and Cardio-Oncology Study Groups of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) in collaboration with the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the ESC have evaluated the current evidence for the value of modern CV imaging in the cardio-oncology field. The most relevant echocardiographic parameters, including global longitudinal strain and three-dimensional ejection fraction, are proposed. The protocol for baseline pre-treatment evaluation and specific surveillance algorithms or pathways for anthracycline chemotherapy, HER2-targeted therapies such as trastuzumab, vascular endothelial growth factor tyrosine kinase inhibitors, BCr-Abl tyrosine kinase inhibitors, proteasome inhibitors and immune checkpoint inhibitors are presented. The indications for CV imaging after completion of oncology treatment are considered. The typical consequences of radiation therapy and the possibility of their identification in the long-term are also summarized. Special populations are discussed including female survivors planning pregnancy, patients with carcinoid disease, patients with cardiac tumours and patients with right heart failure. Future directions and ongoing CV imaging research in cardio-oncology are discussed.

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Introduction

Cardiovascular disease (CVD) and cardiovascular (CV) complications in cancer patients present a growing medical problem, causing substantial morbidity and premature mortality in this population. An increasing prevalence of pre-existing CVD and the CV toxicity of both established and emerging cancer treatments including anthracycline (AC) chemotherapy, targeted therapies such as trastuzumab, proteasome inhibitors (PIs), immune checkpoint inhibitors (ICI) and vascular endothelial growth factor inhibitors (VEGFi), along with biological treatments and radiation therapy collectively contribute to this new epidemic. There is an urgent clinical need to modernize and validate monitoring algorithms for the early detection of CVD in cancer patients receiving potentially cardiotoxic treatments, and to intervene prior to the development of manifest CVD. Considerations are also needed as to which cancer survivors require screening after completion of oncology treatment.

Contemporary cardiac imaging is a valuable instrument to help in multiple ways - for baseline risk stratification, timely diagnosis of early CVD and of cardiac dysfunction, both during and following treatment, for the identification of cancer patients who may benefit from cardioprotective treatments whilst continuing oncology treatment, and prognostication to select cancer patients who may require long term CVD follow up. The Imaging and Cardio-Oncology Study Groups of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) in collaboration with the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the ESC have evaluated the current evidence for the role of CV imaging including echocardiography, cardiac magnetic resonance (CMR), computed tomography (CT) and nuclear testing before, during and after cancer therapy. This position statement summarizes their consensus regarding the application of modern cardiovascular imaging in cancer patients. It focuses on the detection and assessment of myocardial dysfunction and heart failure, the optimal timing

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for monitoring in various cardiotoxic cancer treatments, special populations and future developments in this field. The authors aim to provide cardiologists, oncologists, haematologists and general medical physicians with a framework for using cardiac imaging for the timely diagnosis of CV involvement and for prevention of CVD in cancer patients and survivors. This position statement examines cardiovascular imaging and has been developed in parallel to a position statement addressing the role of cardiac biomarkers in cancer patients (Add reference to HFA Position statement on biomarkers in cardio-oncology) and detailed cancer-treatment specific baseline risk assessment.(1) Cardiovascular imaging and cardiac biomarkers in baseline risk assessment and in surveillance receiving cardiotoxic cancer therapies are synergistic and complementary approaches, and it is important that they should be considered together. A future HFA position statement will review the evidence and provide details of the specific treatment interventions recommended for the different cardiotoxicities detected using CV imaging for a range of cancer therapies. These are complex and beyond the scope of this article.

We emphasize that the suggested surveillance pathways and frequencies of use are based on expert opinion and experience, since validation studies are lacking in this area, especially with regard to cost-effectiveness and effect on long-term outcomes.

General principles

Cardiac imaging in general, and echocardiography in particular, play a central role in the expanding field of cardio-oncology. Given that the current definitions of cardiotoxicity in many guidelines and oncology trials are based on a reduction of left ventricular ejection fraction (LVEF) (2, 3), many oncologists restrict cardiotoxicity evaluation to measurement of this single parameter only. However, it is well known in contemporary cardiology that a normal LVEF does not exclude significant myocardial dysfunction (4, 5). In addition, there

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are important limitations of serial measurement of LVEF such as physiological temporal and operator variability, and haemodynamic load-dependence. Concurrent measurement of blood pressure may help to avoid misinterpretations in cases of blood pressure and blood volume changes due to fluid excess during intravenous chemotherapy or fluid loss due to adverse reactions.(6) Temporal variability of LVEF measured by two-dimensional (2D) echocardiography using biplane Simpson's method has been reported to be approximately 10%, with the same level of 10% seen for inter- and intra-observer variability.(7) Thus, the LVEF should be reassessed to confirm the development of subclinical LV dysfunction (2).

Three-dimensional (3D) echocardiography should be utilized for LVEF and cardiac volumes assessment when available and with appropriate expertise and experience due to its lower inter-, intra-observer and test-retest variability.(7) Adequate inter-reader agreement in an echocardiography laboratory may be achieved by standardizing the analytical approach through dedicated quality audit sessions.(8) 3D echocardiography is likely to become more widely accepted in routine practice due to improved image acquisition and the implementation of semi- or fully automated analysis algorithms.(4) The feasibility of 3D LVEF in breast cancer patients with adequate echocardiographic images was 88% at baseline and 66% after AC therapy, reduced during follow-up due to concomitant radiotherapy, left mastectomy, left breast prosthesis and other patient factors.(9)

When transthoracic echocardiographic image quality is inadequate for the application of Simpson's method, which is more common in cancer patients who have previously undergone left breast or left chest surgery and/or radiotherapy, and sometimes in very cachectic patients, adding contrast media or using alternative imaging modalities such as cardiac magnetic resonance (CMR) can be considered for serial monitoring of LV size and function. The latter technique, although less feasible and more expensive, has improved accuracy and reproducibility with the coefficient of variation for CMR LVEF being reported

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at approximately 4%.(10) The historical method of planar imaging, multigated acquisition (MUGA) scan, used for serial assessment in earlier clinical trials, is not recommended as a first line cardiac imaging modality, due to exposure to ionizing radiation and advances in ultrasound and CMR modalities.(11) Single photon emission computed tomography (SPECT) MUGA acquired with high-sensitivity cadmium zinc telluride cameras can be done with lower radiation dose, faster image acquisition time and improved reproducibility (11).

Global longitudinal strain (GLS) has emerged as a new marker of subclinical ventricular dysfunction demonstrating stronger association with prognosis than LVEF in non-oncology heart disease populations.(12, 13) This reflects the fact that LV longitudinal function may be reduced first and this component of ventricular function has a limited influence upon LVEF (14). Several researchers have reported a higher sensitivity and either a non-inferior or superior test-retest reliability of GLS compared to LVEF (5, 14, 15). A number of observational studies show potential for reduction in GLS to accurately predict a future decrease in LVEF and significant cardiotoxicity. (14, 16, 17)

A recent study in 116 patients with HER2-positive breast cancer supported the serial surveillance using GLS to guide cardioprotection and maintain patients on uninterrupted trastuzumab therapy (18). The ongoing SUCCOUR study is prospectively assessing the value of initiating cardioprotective medication triggered by the reduction of GLS versus waiting for a decline in 3D-LVEF.(19) GLS should be based on 3 apical (long-axis) views and not replaced by single-view longitudinal strain due to substantial disagreement in the diagnosis of cardiotoxicity.(20) Although less feasible and reproducible, 2D- or 3D-derived global circumferential strain may also serve as additional markers of myocardial dysfunction but require more studies for validation (21, 22). GLS surveillance may become a more sensitive strategy for early detection of cardiotoxicity and guide timing of cardioprotective treatment (**Figure 1**).

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Several cardiotoxic cancer treatments including AC and trastuzumab have been shown to cause a persistent reduction in LVEF and GLS (6). Other cancer drugs may cause different forms of myocardial toxicity where LVEF reduction is not the primary manifestation. For example, immune checkpoint inhibitors (ICIs) cause myocarditis, which can lead to severe heart failure, cardiogenic shock and death, but in 38% of cases may also occur even without a fall in LVEF.(23) (24) Thus, decision-making concerning the continuation or interruption of such potentially life-saving therapy should no longer rely solely on the single, surrogate echocardiographic parameter (LVEF) which mainly reflects changes in LV volumes, rather than function.

Several small studies have analysed the serial measurement of LV diastolic function using tissue and transmitral Doppler (E/e') in various cancer populations (25, 26). Most have not found improved sensitivity compared with measurements of LV systolic function for detection of cardiotoxicity. A sequential relation between diastolic and systolic impairment has not been proven, either in experimental, or in clinical settings. Initial investigations of left atrial size and function have shown that early atrial dilation and a reduction in conduit and reservoir strain may be potential markers of cardiotoxicity (27, 28).

Current recommendations of screening for cardiotoxicity using serial LVEF measurement remain sub-optimally implemented in the majority of patients with breast cancer.(29, 30) In one study baseline evaluation was performed in only 74% of patients receiving human epidermal growth factor receptor (HER-2)-targeted therapy, and only 46% were assessed repeatedly during treatment.(31) Quality of care may be improved by establishing dedicated cardio-oncology services delivering structured pathways for baseline risk stratification and surveillance (**Figure 2**).(32, 33)

Assessment of cardiotoxicity risk

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Systematic cardiac surveillance with more sensitive technologies and a higher frequency of measurements will lead to a greater incidence of detected cardiotoxicity.(31) In order to maintain a balance between the rational use of resources and maximal patient safety, we recommend a personalised approach taking into account the patients' baseline risk of cardiotoxicity (see **Table 1**). Cancer patients scheduled to receive potentially cardiotoxic cancer therapies are evaluated pre-treatment for cardiotoxicity risk and stratified into three categories (low, medium and high) according to the baseline CV profile and risk factors, pre-existing CV disease, type and dose of cancer therapy.

New information on the risk of myocardial dysfunction was obtained analyzing follow up data in adult survivors of childhood cancer (34). Even in this relatively young population, the effect size of traditional risk factors for heart failure (HF) including hypertension, insulin resistance, obesity was comparable or even higher than effect size of cancer treatment-related risk factors, such as an AC dose, radiotherapy or current age. Traditional risk factors, including age, coronary artery disease, diabetes, hypertension, atrial fibrillation, renal failure, have also been predominant predictors of prevalent HF or cardiomyopathy in older women (mean age 74 years) after adjuvant trastuzumab therapy (35). If LVEF falls to a marginally normal range (50-54%) before treatment, the incidence of HF rises remarkably in cancer patients receiving AC and trastuzumab (36, 37). New targeted therapies including VEGF tyrosine kinase inhibitors (VEGF-TKIs), second and third generation BCR-ABl TKIs for chronic myeloid leukaemia, and proteasome inhibitors for multiple myeloma, are associated with an increased risk of heart failure and other CV toxicities.

Definitions of cardiotoxicity

The cancer therapy-related cardiac dysfunction (CTRCD) definition, which is adopted in the 2016 ESC Cardio-Oncology position statement, is defined as any reduction of LVEF to

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below 50% or a >10% reduction from baseline falling below the lower limit of normal (2, 3). Current echocardiography recommendations set low normal value of 2D-LVEF as 54% for women and 52% for men (38) and hence in the previous EACVI position statement a reduction of LVEF below 53% was classified as abnormal.(2)

Changes in the myocardial deformation parameter GLS may also be considered an early sign of CTRCD (39-42). When detected it correlates with focal and diffuse fibrosis (43). During follow-up LV GLS falling below (-)18% into the abnormal range (0 to -17.9%) or a >15% relative decrease of this marker and to below the lower limit of normal (LLN) may be considered abnormal (2, 3, 12).

There is a variation in the definition of CTRCD across guidelines, position statements and oncology trials (**Table 2**); numerous mechanisms of cardiotoxicity inherent to different cancer drug classes add to the complexity of this condition. Latest accumulating data on the specific incidence and reversibility of cardiotoxicity have forced the authors to abandon the outdated concept of type I and type II cardiotoxicity (44). The recently proposed Royal Brompton Hospital classification of myocardial toxicity incorporated alterations of biomarkers and/or GLS as evidence of early biochemical, functional or early mixed cardiotoxicity where oncology treatment should continue but consideration to start cardioprotective medication or implement closer monitoring is advised.(32)

CV imaging at baseline pre-treatment

It is essential to evaluate cardiac function with echocardiography before starting potentially cardiotoxic therapy in every cancer patient as a baseline for monitoring and for risk stratification (**Supplemental Figure 1, Supplemental Videos 1A, 1B**). The most relevant parameters for initial and subsequent echocardiographic assessment are presented in **Table 3**. CMR is recommended in cases with poor quality echocardiographic images, in patients with

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complex pre-exisiting heart diseases (for example hypertrophic or dilated cardiomyopathy). In patients with suspected angina stress echocardiography, vasodilator stress CMR or single photon emission computed tomography (SPECT) are recommended to diagnose the presence and extent of myocardial ischemia and assess the need for anti-anginal medications or alternative treatment. In patients with chest pain but no history of coronary disease, CT coronary angiography is recommended as an alternative to functional testing.(45)

Echocardiography during anthracycline chemotherapy

Before starting AC therapy, we recommend classifying the cardiotoxicity risk as low, medium or high according to therapy-related and patient-related factors (**Table 1**). The incidence of cardiac events during next 10 years after AC therapy accounts for 2-5% in the medium-risk and >5% in the high-risk group (39). This empirical approach aims to personalize echocardiographic surveillance (**Table 4, Figure 3**), including 3D-LVEF and GLS when available, intensifying follow-up in high risk patients and reducing frequency in low risk patients. In AC cardiotoxicity most cases occur during the first year after completion of chemotherapy, and therefore assessments at 6 and/or 12 months post completion of chemotherapy should be considered.(46) (see **Table 4, Figure 4, Supplemental Figure 2, Supplemental Videos 2A, 2B, 2C, 2D, 3A, 3B, 3C**). Variable remodeling responses to anthracycline chemotherapy can occur, including cardiomyocyte atrophy with reduced LV mass and dysfunction but relative preservation of LVEF.(47)

In the long-term follow up after completion of cancer therapy repeated surveillance echocardiographic evaluation is recommended in selected populations such as young patients who received high total cumulative AC doses (>400mg/m^2 doxorubicin or equivalent), patients with significant pre-existing CVD, female cancer survivors planning to become pregnant or at the end of the first trimester of pregnancy,(48) and survivors who are planning

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to compete in high intensity exercise, for example, marathons, endurance cycling, triathlons.(49)

Echocardiography during HER2-targeted treatment (trastuzumab, pertuzumab, T-DM1, lapatinib, neratinib)

In patients on HER2-targeted therapies, standard surveillance according to the product license includes echocardiography at baseline (with 3D-LVEF and GLS if available) and every 3 months during therapy (50, 51). Similar to the monitoring during AC described above, we suggest taking into account baseline risk of cardiotoxicity with a frequency of surveillance personalized to this baseline risk (see **Table 5, Figure 5**).(35, 36) The same frequency of imaging is recommended for patients starting trastuzumab alone, trastuzumab and pertuzumab, ado-trastuzumab or Trastuzumab emtansine (T-DM1) or oral HER2-targeted therapies. There are also important considerations for the different cancer populations (early invasive versus metastatic HER2 positive breast cancer, HER2 positive gastric cancer).

The evidence for long term follow-up echocardiography in patients following adjuvant HER2 targeted therapies for early invasive breast cancer is limited. Low risk patients who are asymptomatic may not require any follow up imaging, but a single review at 6-12 months following the final cycle may be considered if they have also received neoadjuvant or adjuvant AC. In asymptomatic patients with medium or high baseline cardiotoxicity risk, a follow up echocardiogram and clinical assessment should be considered 3-6 months and 12 months after the final dose of HER2-targeted treatment (see **Table 5, Figure 5**). Any patient who has new LV impairment or cardiotoxicity during HER2-targeted therapy will require follow up assessment after starting any cardiac treatment to assess function and safety to continue HER2-targeted therapies, and at completion of treatment to assess for recovery and guide weaning of cardiac medication.

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In asymptomatic patients who require long-term treatment in the setting of metastatic disease, echocardiography is recommended with the same frequency as for adjuvant trastuzumab during year 1, and then less frequent if cardiac biomarkers and LV function remain normal, e.g. 4 monthly in year 2 and 6 monthly thereafter in low risk patients.(52) Surveillance should continue at the same frequency if disease progression requires switching from trastuzumab and pertuzumab to T-DM1.(53) If new cardiotoxicity or cardiac symptoms develop then more frequent monitoring is recommended.

Echocardiography during VEGFi and BCR-Abl tyrosine kinase inhibitor treatment

LV dysfunction occurs in 5-10% of patients receiving VEGFi TKIs and 2-10% of patients receiving 2nd and 3rd generation BCr-Abl TKIs due to a direct myocardial toxicity, uncontrolled hypertension and exacerbation of pre-existing CVD (43, 54-60). In the absence of prospective studies providing evidence, it is the opinion of the authors that echocardiography should be considered every 4 months during the first year in all patients receiving these treatments, with an additional early assessment 2-4 weeks after starting treatment in patients with high baseline CV risk (61). In patients who require long-term treatment with VEGFi or 2nd and 3rd generation BCR-Abl TKIs 6-12 monthly echocardiography should be considered, as long as they remain asymptomatic and without clinical events during the first year. In patients who are candidates for dasatinib for chronic myeloid leukaemia pretreatment echocardiography screening to assess for pre-existing pulmonary hypertension is recommended, as well as maintaining a low threshold for repeat echocardiography if cardiac symptoms develop (62). The decision to stop the treatment if new pulmonary arterial hypertension is detected may require right heart catheterization in selected cases.(63)

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Echocardiography during proteasome inhibitor treatment

Proteasome inhibitors (PIs) including bortezomib, carfilzomib and ixazomib are targeted therapies for multiple myeloma (MM). Bortezomib introduces a modestly increased risk for cardiac disorders in a meta-analysis by the Cochrane group compared to control (OR 1.74, CI 1.17-2.58)(64). Carfilzomib, which is an irreversible PI, has a higher risk of CV toxicity including myocardial infarction (MI) and LV dysfunction, as well as increased incidence of total symptomatic HF (7.1 vs 4.1%) and HF categorized as grade ⩾3 adverse reaction (4.3 vs 2.1%) compared to control in the ASPIRE study.(65) Combined CV toxicities including HF were more frequent in MM patients receiving carfilzomib compared to bortezomib in the ENDEAVOR study (66). A recent study reported CV toxicity rates in 95 MM patients receiving either carfilzomib (n=65) or bortezomib (n=30). At a follow up of 18 months 50% of carfilzomib-treated and 17% of bortezomib-treated MM patients had a significant clinical CV event, with new heart failure most common, and worse overall survival in the MM patients with CV events.(67) Given these high CV event rates baseline echocardiography is advisable in all MM patients scheduled to receive a PI, which also allows assessment for cardiac AL amyloidosis. Surveillance may be considered in medium/high risk patients receiving carfilzomib. Prompt echocardiography is strongly recommended if MM patients receiving PI therapy presenting with new cardiac symptoms and signs. The ENDEAVOR trial echocardiography sub-study reported limited utility for serial echocardiographic screening as a risk mitigation tool in unselected patients receiving carfilzomib. However, the evaluation was limited to 4 parameters (LVEF, estimated pulmonary artery pressure, tricuspid annular plane systolic excursion [TAPSE] and right ventricular [RV] fractional area change [FAC]) and less than 50% of patients completed the echocardiogram surveillance protocol limiting its validity (68).

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Echocardiography during immune checkpoint inhibitor treatment

Immune checkpoint inhibitors (ICI) have improved clinical outcome and overall survival in cancer patients with various metastatic malignancies. CV toxicity associated with ICI (e.g. ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab), including myocarditis sometimes causing cardiogenic shock (69) and/or malignant ventricular tachyarrhythmias, pericarditis (including effusion and tamponade), arrhythmias, and non-inflammatory LV systolic dysfunction, was initially considered rare (<1%) but with expanding use its incidence is increasing.(70, 71) ICI-mediated fulminant myocarditis is relatively rare but has been associated with a high mortality rate (25-50%).(24) The echocardiographic findings may vary from a normal examination to reduced wall thickening, reduced GLS, regional and global wall motion abnormalities and/or diastolic dysfunction (72-74). Serial echocardiographic screening may be considered in patients at high risk (combination ICI, ICI in combination with a second oncology drug with known cardiotoxicity, significant pre-existing heart disease e.g. heart failure, cardiomyopathy). A recent study suggests a reduction in GLS is an early sign of ICI-induced myocarditis.(23) The timing and duration of surveillance remains to be determined as severe myocarditis and pericarditis usually appear early (within first 4 cycles) whereas non-inflammatory LV dysfunction emerges later (24).

Cardiac magnetic resonance imaging during cancer therapy: why and when?

The routine use of CMR in cardio-oncology for surveillance is not feasible due to the lack of widespread accessibility and relatively high cost. However, when available, it is a very useful tool to identify changes in ventricular volumes and EF, especially in patients with poor quality echocardiographic images if a discrepancy between measurements of LV function exists, or if myocardial perfusion assessment for ischaemia is simultaneously planned.(39,

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43) CMR also offers helpful information regarding the presence of prior myocardial infarction scar, diffuse fibrosis and intracellular or interstitial edema (T1 mapping with extracellular volume fraction quantification and T2STIR) during cancer treatment, facilitating our understanding of the pathogenesis of cardiotoxicity from the different cancer drug classes and radiation (75-77). Recent data suggest that novel CMR indices may be potentially the earliest markers of AC-induced damage: an intracellular water life time τ_{ic}, related to the size of cardiomyocyte,(47) and a prolongation of T_2 relaxation time, correlated with intra-cardiomyocyte oedema.(78)

CMR is particularly important for cancer patients receiving ICI with new cardiac symptoms, arrhythmias or cardiac troponin elevation when ICI-mediated myocarditis is suspected. (79) Additionally, CMR is an excellent test for the comprehensive evaluation of pericardial diseases, cardiac masses, infiltrative (amyloidosis) as well as storage diseases (80, 81).

Cardiac nuclear imaging during cancer treatment

In a retrospective study of Hodgkin's lymphoma patients receiving AC-containing chemotherapy serial [^{18}F]fluorodeoxyglucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-CT) scans showed an increase in cardiac FDG uptake, which was associated with a decline in LVEF.(82) Increased myocardial glucose utilization has also been observed after trastuzumab and radiation therapy, probably linked to myocardial inflammation and cell damage (11). Given the common use of ^{18}F-FDG PET to monitor cancer progression, this phenomenon of elevated ^{18}F-FDG uptake might be exploited for cardiotoxicity surveillance. If echocardiography and CMR are not available, then SPECT MUGA may be used to measure LVEF.

Cardiac FDG-PET can be used to assess for ICI-mediated myocarditis in cases where CMR is not available, contraindicated or provides equivocal results. There are also indications for

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nuclear imaging studies where a specific tracer can evaluate for the presence of cardiac metastases, for example, radiolabeled octreotide for cardiac carcinoid metastases.

CV imaging in first year after completing cancer treatment

Echocardiography is recommended during follow up in cancer patients who developed new CTRCD or other CV toxicities requiring initiation of CV therapy during cancer therapy. The timing will depend upon several variables including the type of treatment (AC chemotherapy, HER2 targeted therapy, PI, VEGFi, 2nd and 3rd generation BCR-ABl TKI, ICI), nature and severity of the CV toxicity and underlying status of their cancer and overall prognosis. All patients started on CV therapies (ACEi, BB, ARB, MRA) for new LV dysfunction should have an echocardiogram 3-6 months after completing cancer treatment, whilst continuing cardiac medication before weaning CV medication. CMR may be indicated to assess response to treatment following systemic therapy, radiotherapy and/or surgery to cardiac tumours.

CV imaging during and after radiation therapy

Radiotherapy (RT) including the heart in the radiation field (mediastinal, left breast or left chest) can affect the heart structures and induce the excess of CV morbidity and mortality in cancer survivors. The prevalence of CTRCD increases linearly with the mean heart radiation dose; the risk can be potentiated by the adjunctive AC and interaction with pre-existing CV disease (83). Long term CTRCD include valvular heart disease, constrictive pericarditis, cardiomyopathy, coronary artery disease, arrhythmias, autonomic dysfunction, carotid artery disease and other vascular disease.

Echocardiography

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Echocardiography can assess left and right ventricular function, pericardial constriction and effusion and valvular disease (84). Pericardial changes are the most frequent RT-induced CV abnormality and can develop months to years after completion of RT (85, 86). Echocardiography is useful for evaluation of the presence and quantification of pericardial effusion and the presence of constrictive physiology (87).

Cardiomyopathy with a decrease in left and right ventricular function is the result of cell loss and myocardial fibrosis induced by high doses of RT. RT exposure to the heart of ≥15 Gy is associated with an increased risk of cardiotoxicity in comparison with non-irradiated survivors, especially in combination with AC (**Figure 6, Supplemental Videos 4A, 4B, 4C**).(88) Even lower doses of radiation to the heart in left breast cancer patients can interact with pre-existing CV disease increasing the risk of HF including cases with preserved EF (HFpEF) (3).

Valvular disease can be caused by a fibrotic process within the valvular apparatus which can result in leaflet thickening, fibrotic changes, shortening and calcifications, predominantly in left-sided valves with subsequent development of stenosis or insufficiency. Typically, alterations involve the base and mid-portions of the mitral valve leaflets, sparing tips and commissures. The incidence of valve disease increases significantly after 20 years following RT, and linearly with the RT dose, therefore careful evaluation of valves structure and function in serial echocardiography should be considered. The reasonable time of examination in asymptomatic cases may be at 5 years in high risk patients and at 10 years in rest of the patients followed by 5 yearly echocardiography.

CT coronary angiography and calcium score

Radiation-related coronary artery disease (CAD) is observed 5 years and beyond after RT (89). Cancer survivors have a more rapid progression of pre-existing atherosclerosis (90, 91),

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indicating a potential need for earlier and more aggressive approach in older patients with known CAD or risk factors (**Supplemental Figure 3**). Conversely, in younger cancer survivors a specific radiation-induced coronary disease, which is different from atherosclerosis, may develop following exposure to high radiation doses. Therefore, the role of surveillance computed tomography coronary angiography (CTCA) to detect subclinical CAD has been proposed.

As in the general population, in RT survivors the accuracy of CTCA and calcium score in the diagnosis of significant CAD is high and demonstrates excellent negative predictive value (92-94). Moreover, recent data show that the inclusion of CTCA in the diagnostic workup of stable patients improves long-term prognosis by reducing the incidence of MI (94). However, the timing of CTCA for surveillance in asymptomatic cancer survivors following high dose radiation to the chest is unknown and requires further study.

Incidental coronary calcium in thoracic CT for staging and/or RT planning, subsequent follow-up CT and/or PET-CT scans should be reported and quantified according to recent recommendations from Society of Cardiovascular Computed Tomography (95). Coronary artery calcification (CAC) obtained from non-gated chest CT scans correlates well with a 3 mm CAC scan and is incrementally associated with worse CV outcomes in cancer patients (96) implicating timely prescription of preventive therapies.

CV imaging in specific cancer populations

1. *Cancer patients with pulmonary artery hypertension and/or RV dysfunction*

Data on RV remodeling and dysfunction in oncology patients remain scarce. There are particular cardiotoxic cancer treatments that may specifically cause PAH [dasatinib (97)] and/or RV dysfunction [AC (98), trastuzumab (99), cyclophosphamide (100) and dasatinib (97)]. A significant reduction of RV longitudinal strain has been shown within 3 months of

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the commencement of AC therapy (101). RV circumferential strain, assessed by CMR, decreased after 6 months of trastuzumab use in a cohort of HER2+ breast cancer patients (102).

RV function and pulmonary artery pressure should be assessed at pre-treatment baseline and subsequently during echocardiographic surveillance (see **Table 3**). The frequency of scanning depends upon the severity of the pre-existing PAH or RV dysfunction and the risk of cardiotoxicity analogously to the monitoring of LV systolic dysfunction (see **Tables 4** and **5**). Conventional 2D echocardiographic measurements such as RV fractional area change or tricuspid annular plane systolic excursion (TAPSE) are recommended.(101) The European Association of Cardiovascular Imaging suggests routine measurement of RV free wall strain, which is more representative of RV longitudinal deformation than septal strain (103); recent advances in 3D quantification makes the estimation of RV ejection fraction possible not only by CMR but also by 3D echocardiography.(104)

2. Cardiac masses

Echocardiography as initial imaging modality for the diagnosis of cardiac tumours provides important information regarding their location, size, attachment, mobility, echogenicity, calcification and potential mechanical complications, for example, valve obstruction (**Supplemental Video 5A**) (105). Nonbacterial thrombotic endocarditis is one of the findings, frequently associated with adenocarcinomas of the lung, ovary, gastrointestinal system (106). Real-time 3D echocardiography by transthoracic or transoesophageal approach provides more accurate assessment of tumour mass (volume), homogeneity, vascularity or necrosis (**Supplemental Video 5B)** (107). Contrast echocardiography improves definition of intra-cavity structures and may help distinguish between vascular and perfused tumour versus non-perfused thrombus including chemotherapy infusion line-related right atrial thrombus (108, 109).

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CMR and CT are excellent tools for mass tissue characterization and evaluation of perfusion. A CMR protocol includes black-blood T1- and T2-weighted imaging with or without fat tissue suppression before and after injection of gadolinium (110). Cardiac metastases appear as single or multiple masses with associated oedema in a patient with a known primary malignancy elsewhere. Compared with benign, malignant primary cardiac tumours are rare, larger, more frequently located in the right heart and pericardium, typically hyperintense on T2-weighted images, demonstrate vascularity on first-pass perfusion and are more likely to have positive late gadolinium enhancement (111, 112). Primary cardiac lymphoma may show features of diffuse infiltration into the myocardium on contrast images and sign of "floating artery", when epicardial vessels are encased by tumour but remain patent.(113) Advanced CMR techniques such as parametric mapping or fat-water separation may help in differentiation from benign conditions such as lipomatous hypertrophy of the interatrial septum (114, 115).

CT scanning can distinguish fat and calcium components and detect the relationship of a mass to adjacent structures including the coronary and pulmonary vessels (116, 117). Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) isotope can also be used to characterize cardiac masses or detect metastases if diagnostic uncertainty exists or if CMR is contraindicated (118).

3. Cardiac amyloidosis

Cardiac amyloidosis is an infiltrative disease in which the extracellular space of myocardium is expanded by the deposition of abnormal protein known as amyloid (119). Most cases of amyloid involvement of the heart are either transthyretin (ATTR) type or immunoglobulin-derived light-chains (AL) from an underlying MM or lymphoproliferative malignancy (120).

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Standard echocardiography typically shows all or some of the well-known characteristic features including LV wall thickening with normal or reduced LV volumes, enlarged atria, increased thickness of right ventricular wall and cardiac valves, loss of drop of interatrial septum and pericardial or pleural effusion. Symmetric hypertrophy is generally related to AL amyloidosis whereas asymmetric patterns are found in 80% of ATTR amyloidosis (121). Due to extensive amyloid deposits, myocardial texture may develop a "sparkling" appearance, although this is hard to recognize during harmonic imaging and more readily appreciated during fundamental imaging. Functional assessment may reveal normal or impaired LV systolic function, left or bi-atrial dilatation and restrictive LV filling pattern (40, 122). Myocardial deformation analysis using speckle tracking echocardiography or CMR tissue tracking imaging shows significantly reduced global LV longitudinal strain, with more evident decrease of segmental strain in the basal and mid-ventricular zones compared to the apical area - a feature known as "apical sparing" (42, 123-127).

CMR typically demonstrates a combination of global subendocardial, diffuse transmural or patchy late enhancement in a non-coronary distribution with a dark blood pool. Difficulties in nulling the myocardium when defining correct inversion time is another characteristic finding (128, 129). Both types of cardiac amyloidosis significantly increase native T1 relaxation time and extracellular volume (ECV), which can be estimated using CMR parametric mapping (130, 131).

^{99m}Technetium labelled pyrophosphate (^{99m}Tc-PYP) and 3,3-diphosphono-1,2-propanodicarboxic acid (^{99m}Tc-DPD) accumulate in myocardium infiltrated by TTR amyloid, whereas hearts with AL deposits demonstrate ^{18}F-florbetapir uptake (132, 133), with no or minimal ^{99m}Tc-DPD uptake. Positive ^{99m}Tc-PYP or ^{99m}Tc-DPD scan is specific for the ATTR diagnosis and in combination with CMR and absence of monoclonal protein band may be sufficient to confirm ATTR cardiac amyloidosis without the need for cardiac biopsy (134).

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4. *Carcinoid cardiac disease*

Carcinoid tumours can secrete vasoactive substances causing a "carcinoid syndrome" in the setting of liver or pulmonary metastases.(135) Carcinoid-related serotonin is deposited in the right heart endocardium and both tricuspid and pulmonary valves causing fibrosis.(136) Typical echocardiographic features in more than 50% of patients of carcinoid include retracted, shortened and thickened leaflets of both tricuspid and pulmonic valves.(137) The leaflets appear fixed and usually there is a significant coaptation gap leading to severe or torrential tricuspid and pulmonary regurgitation. Subsequently, volume and pressure overload develop causing hypertrophy and dilation of the right chambers. Less commonly, there may be a tricuspid or pulmonary stenosis.(138) Further cardiac imaging with high sensitivity and specificity include SPECT-CT with ^{111}Indium-labelled octreotide and PET-CT with ^{68}Gallium-labelled octreotide to examine for myocardial carcinoid metastases which are present in ~4% of carcinoid patients.(139, 140) In a minority of cases (~15%) in patients with pulmonary metastases, an intracardiac shunt can be detected; (138) in the presence of high levels of vasoactive substances, left sided heart valves may also be affected. Expert opinion regarding surveillance for development and progression of carcinoid valvular heart disease recommends 6 monthly echocardiography in asymptomatic patients with metastatic carcinoid syndrome and an elevated NT-proBNP.(141)

Future directions and imaging technologies

The important question is how to alter the management of cancer patients in whom new abnormalities of cardiac function are detected with imaging. This is complex and will depend upon many variables including pre-existing CV disease, pre-existing cardiac medication, current CV physiological parameters, the cause and severity of the cardiotoxicity, the planned duration of ongoing treatment and patient preferences. Some guidance has been provided

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following new changes in GLS and or biomarkers in a real world cardio-oncology clinic (32). This topic will be addressed in a future HFA cardio-oncology position statement.

The main challenge in creating CV imaging surveillance recommendations is the lack of scientific evidence from randomized clinical trials. The ongoing SUCCOUR study will provide crucial data on the value of strain imaging for early detection of cardiotoxicity comparing to the conventional measurement of LVEF for timely guidance of cardioprotective treatment.(19) Among the endpoints of the study are not only the risk of cardiac dysfunction and heart failure development, but also the completion rate of the planned chemotherapy.

An advanced strain-encoded (SENC and fast-SENC) CMR tagging technology provides high accuracy and reproducibility during single heartbeat acquisitions without contrast and may be helpful in the future to detect early cardiotoxicity.(142) The PROACT study with mixed blinded and unblinded design will include breast cancer, lymphoma and sarcoma patients receiving AC chemotherapy, also aiming to initiate cardio-protection at the earliest possible moment (**Figures 7, 8**).(143) ~~Baseline fast-SENC evaluation is used to stratify participants into groups with lower and higher risk of the future cardiac toxicity.~~ Also, a decrease of native T1 times as early as 48 h after first AC cycle has been shown to predict the development of CTRCD after completion of chemotherapy. (144)

Other recent hypotheses incorporate the use of baseline myocardial ^{18}F-FDG uptake (82) and machine learning models for prediction of cancer therapy-induced cardiotoxicity.(145) PET-CT protocols combining oncology and cardiology questions may be informative; LV mass reduction is suggested as a potential marker of CTRCD.(146) For the design of imaging trials, the standardization of image acquisition, evaluation, reporting, as well as staff training, blinded review and regular quality assessment are key considerations.(147)

Future research should focus on the best timing of cardiac imaging during and after particular types of cancer therapy in different patient populations. Pragmatic and registry-based clinical

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trials may be helpful, with individual or cluster randomization by clinic or hospital. Observational studies to explore big data bases including information on time and result of imaging tests with concomitant changes in cancer and CV therapy would be of great value. One of the most important questions is whether meticulous monitoring by echocardiography and biomarkers improves the mortality and morbidity of cancer patients. The consequences of cancer therapy interruptions and the cost-effectiveness of surveillance should be analyzed. Preventive strategies aimed at treating all oncology patients do not seem practical to most clinicians at the present time due to the potential for substantial overtreatment and the high relative cost.

Conclusions

Cardiovascular imaging modalities demonstrate a remarkable progress in the developing field of cardio-oncology providing highly sensitive methods for timely diagnosis of cardiotoxicity. Myocardial deformation imaging and three-dimensional volumetric analysis seem to be optimal techniques to address temporal structural and functional changes during cancer therapy. The intensity of echocardiographic monitoring should be based on the individual risk of cardiotoxicity, coordination with cardiac biomarkers monitoring, and requires collaborative evaluation by the cardio-oncology team. Suggested detailed algorithms for anthracycline and HER2-targeted therapies aim to improve current clinical practice. Further studies are needed to establish effective surveillance schemes changing the outcomes of oncology patients.

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Table 1. Assessment of cardiotoxicity risk

<table>
<tr><th>Therapy-related factors</th><th>Patient-related factors</th></tr>
<tr><td colspan="2">Low risk of cardiotoxicity</td></tr>
<tr><td>Lower dose AC (e.g. doxorubicin <200 mg/m^2, epirubicin <300 mg/m^2), liposomal formulations</td><td rowspan="2">Age >18 and <50 years</td></tr>
<tr><td>Trastuzumab without AC</td></tr>
<tr><td colspan="2">Medium risk of cardiotoxicity</td></tr>
<tr><td rowspan="2">Modest-dose AC (doxorubicin 200-400 mg/m^2 and epirubicin 300-600mg/m^2)</td><td>Age 50-64 years</td></tr>
<tr><td rowspan="5">1-2 CV risk factors such as hypertension, dyslipidemia, obesity, insulin resistance, smoking</td></tr>
<tr><td>AC followed by trastuzumab</td></tr>
<tr><td>VEGF Tyrosine kinase inhibitors</td></tr>
<tr><td>2nd and 3rd generation BCR-ABL Tyrosine kinase inhibitors</td></tr>
<tr><td>Proteasome inhibitors</td></tr>
<tr><td>Combination immune checkpoint inhibitors</td><td></td></tr>
<tr><td colspan="2">High risk of cardiotoxicity</td></tr>
<tr><td>Simultaneous AC and trastuzumab</td><td>Age ≥65 years</td></tr>
<tr><td>High-dose AC (doxorubicin ≥400 mg/m^2 or epirubicin ≥600 mg/m^2)</td><td>>2 CV risk factors as hypertension, dyslipidemia, obesity, smoking</td></tr>
<tr><td>Modest-dose AC plus left chest radiation therapy</td><td>Diabetes</td></tr>
<tr><td>Elevated cardiac troponin post AC prior to HER2 targeted therapy</td><td rowspan="2">Underlying CV disease: CAD, PAD, CMP, severe VHD, heart failure</td></tr>
<tr><td>High-dose radiation therapy to central chest including heart in radiation field ≥30 Gy</td></tr>
<tr><td rowspan="2">VEGF Tyrosine kinase inhibitors following previous AC chemotherapy</td><td>Reduced or low-normal LVEF (50-54%) pre-treatment</td></tr>
<tr><td>Prior cancer therapy</td></tr>
</table>

ABR – active BCR-related, AC – anthracyclines, BCR – breakpoint cluster region, CAD – coronary artery disease, CMP – cardiomyopathy, CV – cardiovascular, Gy – gray, LVEF – left ventricular ejection fraction, PAD – peripheral artery disease, VEGF – vascular endothelial growth factor, VHD – valvular heart disease

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Table 2. The difference in published definitions of cardiotoxicity

	ESC (1)	EACVI/ASE (2)	ESMO/CREC (3)	ASCO (4)	CTCAE (5)	FDA (7)*
Cut-off for ejection fraction	<50%	<53%	<55%	<55%	<50%	-
Change in ejection fraction (absolute reduction)	>10% decline from baseline	>10% decline from baseline	decline ≥5% to less than 55% with symptoms, or decline ≥10% to below 55% without symptoms	-	Grade 2 (resting EF 40-50%; 10-19% drop from baseline); Grade 3 (resting EF 20-39%; >20% drop from baseline); Grade 4 (resting EF <20%)	>20% decrease if EF remained normal, or >10% decrease if EF is less than normal
Global longitudinal strain (GLS)	Relative reduction in GLS>15% from baseline	Relative reduction in GLS>15% from baseline	-	Relative reduction in GLS>15% from baseline	-	-

*for anthracyclines; ESC - European Society of Cardiology EACVI – European Association of Cardiovascular Imaging
ASE – American Society of Echocardiography
ESMO - European Society of Medical Oncology
ASCO – American Society of Clinical Oncology
CTCAE – Common Terminology Criteria for Adverse Events (US Departments of Health and Human Services)
CREC – Cardiac Review and Evaluation Committee
FDA – Food and Drug Administration (US)

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Table 3. Parameters relevant for cardio-oncology surveillance: echocardiography protocol

Parameters	Clinically significant changes	Comments
Left ventricular size and function		
LV EF by Simpson's 2D, or (semi)automatic 3D	Drop >10% (percentage points) for 2D, >5% for 3D from pre-treatment value	Decline of LVEF to value <40-50% suggests initiation of cardioprotection
2D/3D GLS, GCS	Relative reduction by >10-15% from pre-treatment value and to below lower limit of normal	Average from 3 apical views; do not use single-view value
LV 2D/3D systolic and diastolic volumes	Increase by 15 ml for ESV, 30-35 ml for EDV	Increase in volumes reflects remodelling and fluid status
Right ventricular function, pulmonary artery pressure and volemia		
Markers of systolic RV function	TAPSE <1.7 cm, FAC <35%, RV free wall strain <20%, 3D RV EF <45%	Show prognostic value in heart failure and pulmonary hypertension
Velocity of tricuspid regurgitation (TR)	Peak systolic TR velocity >2.8 m/s	Indicates probable pulmonary hypertension
IVC diameter, collapse on inspiration	Dilatation >2.1 cm or narrowing <1.3 cm	Relates to hypervolemia or dehydration, respectively

EF – ejection fraction, EDV – end-diastolic volume, ESV – end-systolic volume, FAC – fractional area change, GLS – global longitudinal strain, GCS – global circumferential strain, IVC – inferior vena cava, LV – left ventricular, RV – right ventricular, TAPSE – tricuspid annulus plane systolic excursion

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Table 4. Echocardiographic surveillance during and after anthracycline chemotherapy

BASELINE RISK OF CARDIOTOXICITY	DURING CHEMOTHERAPY	FOLLOWING CHEMOTHERAPY
LOW	• Baseline • Following cycle completing cumulative lifetime dose of 240 mg/m^2 Doxorubicin or equivalent* • Every additional 100 mg/m^2 Doxorubicin above 240 mg/m^2 or every 2 cycles	• 12 months after final cycle • 5 yearly review
MEDIUM	• Baseline • Following 50% of planned total treatment or every 2 cycles (optional) • Following cycle completing cumulative lifetime cycle of 240 mg/m^2 Doxorubicin or equivalent*	• 12 months after final cycle • 5 yearly review
HIGH	• Baseline • Every 2 cycles • Consider after every cycle above 240 mg/m^2 Doxorubicin or equivalent **	• 6 months after final cycle*** • 12 months after final cycle • annually for 2 or 3 years thereafter and then in 3- to 5-year intervals for life

CV - cardiovascular, cycle = chemotherapy infusion

* 240mg/m^2 Doxorubicin is equivalent to 360mg/m^2 Epirubicin, 320mg/m^2 Daunorubicin and 50mg/m^2 Idarubicin

**300mg/m^2 Doxorubicin is equivalent to 420mg/m^2 Epirubicin, 400mg/m^2 Daunorubicin and 60mg/m^2 Idarubicin

*** Depending upon symptoms and evidence of new LV dysfunction during treatment

NB all low and medium CV risk cancer patients who develop new cardiac symptoms or new LV dysfunction during treatment are reclassified as high CV risk and if chemotherapy continues, they should follow the high-risk surveillance

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Table 5. Echocardiographic surveillance during and after HER2-targeted therapies

	BASELINE RISK OF CARDIOTOXICITY	DURING HER2-TARGETED THERAPIES	FOLLOWING COMPLETION OF HER2-TARGETED THERAPY
EARLY INVASIVE HER2+ BREAST CANCER WITH NEOADJUNVANT OR ADJUVANT TRASTUZUMAB*	LOW	• Baseline • Every 4 cycles	• Optional 6-12 months after final cycle
	MEDIUM	• Baseline • Every 3 cycles then reduce to every 4 if stable at 4 months***	• 6 months after final cycle • Optional 12 months after final cycle
	HIGH	• Baseline • Every 2 cycles then reduce to every 3 if stable at 3 months ****	• 3 and 12 months after final cycle • Optional 6 months after final cycle
METASTATIC HER2+ BREAST CANCER OR GASTRIC CANCER WITH LONGTERM HER2-TARGETED THERAPIES**	LOW	• Baseline • Every 4 cycles in year 1 and every 6 cycles in year 2 and then reduce frequency to 6 monthly	Not indicated unless symptomatic
	MEDIUM	• Baseline • Every 3 cycles then if stable reduce to 6 monthly***	Not indicated unless symptomatic
	HIGH	• Baseline • Every 2 or 3 cycles for 3 months, then reduce to every 4 cycles in year 1, the reduce frequency ****	Not indicated unless symptomatic

CV - cardiovascular, cycle = chemotherapy infusion

* Neoadjuvant trastuzumab or trastuzumab and pertuzumab

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** Long term trastuzumab, trastuzumab and pertuzumab, or T-DM1

*** Choice of 2 or 3 depends upon variables including baseline LV function, CV history, baseline troponin and previous AC chemotherapy. In patients starting which surveillance after first 2 cycles reducing to every 3 and then every 4 from 6-12 months (and thereafter in metastatic patients) if asymptomatic and LV function stable is recommended.

**** In high-risk patients close surveillance every 2 cycles is recommended for the first 4 cycles and then reducing to every 3 cycles for the remainder of the first year of treatment. For high risk patients with metastatic HER2+ breast cancer requiring long term treatment we recommend a reassessment at 12 months to then guide long term frequency of surveillance depending upon symptoms, new LV dysfunction and prognosis.

NB all low and medium CV risk cancer patients who develop new cardiac symptoms or new LV dysfunction during HER2-targeted treatment are reclassified as high CV risk and if HER2-targeted therapy continues they should follow the high-risk surveillance.

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Figure 1. General principles of imaging for cardiotoxicity. BP – blood pressure, CMR – cardiac magnetic resonance, GLS – global longitudinal strain, LV – left ventricle.

Figure 2. Cardio-oncology interactions

Figure 3. A surveillance pathway using biomarkers and echocardiography for cancer patients receiving 6 cycles of anthracycline chemotherapy with timing based upon baseline cardiovascular risk. Pathways for low risk (black), medium risk (red) and high risk (blue) are presented. B - baseline pre treatment, C - cycle of chemotherapy, M - months post final cycle. * optional additional assessment timepoints.

Figure 4. A case of 66-year-old female with invasive breast ductal carcinoma (ER+HER2+) treated by the combination of doxorubicin, cyclophosphamide, paclitaxel, radiotherapy (35Gy+10) and Trastuzumab. **(A)** Baseline apical 2D echocardiographic 4-, 2- and 3-chamber views, showing normal left ventricular ejection fraction, with speckle tracking-derived bull's eye and normal global longitudinal strain (GLS). **(B)** Baseline 3D volumetric analysis of left ventricle and left atrium; measurements are normal. **(C)** At 3 months follow up 2D left ventricular ejection fraction remains normal, while 3D ejection fraction drops by 10% and GLS by 19%. This entailed the initiation of anti-remodeling treatment with no interruption of oncologic drugs. **(D)** At 6 months follow up while continuing cancer and cardiac medications the 3D ejection fraction reversed by 5%, and GLS recovered by 10%.

Figure 5. A surveillance pathway using biomarkers and echocardiography for patients receiving neoadjuvant anthracycline chemotherapy (doxorubicin or epirubicin) and trastuzumab followed by 12 months of adjuvant trastuzumab for HER2+ early breast

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cancer with timing based upon baseline cardiovascular risk. Pathways for low risk (black), medium risk (red) and high risk (blue) are presented. AC – anthracycline chemotherapy, B - baseline pre-treatment, C - cycle of chemotherapy or adjuvant trastuzumab, Cn - neoadjuvant cycle of trastuzumab, M - months post final cycle, PAPT - post anthracycline chemotherapy pre trastuzumab, * and ** optional additional assessment timepoints.

Figure 6. A case of 44-year-old male in NYHA III functional class. He had a history of Hodgkin lymphoma at the age of 19 treated with Doxorubicin, Bleomycin, Vinblastine, Dacarbazine (ABVD) and mediastinal radiation. **(A)** 2D echocardiography with speckle tracking showed severe systolic dysfunction: low left ventricular ejection fraction and global longitudinal strain (GLS). Medical heart failure treatment (sacubitril/valsartan, bisoprolol, eplerenone, furosemide) and cardiac rehabilitation were administered. **(B)** 3D left ventricular ejection fraction was equal to 30%. **(C)** After 6 months a significant improvement of 2D, 3D left ventricular ejection fraction and GLS is observed in parallel with a shift to NYHA I functional class.

Figure 7. A case of 58-year old female suffering from HER2 positive right breast cancer with a high baseline risk of cardiotoxicity. Cardiac magnetic resonance (CMR) exams including Fast-SENC MyoStrain testing were performed at baseline and 5 follow-up intervals through 390 days after initiation of chemotherapy with no signs of cardiac damage. The graph shows % normal MyoStrain (≤ -17%) in black with CMR LVEF in green and echocardiography LVEF in red. MyoStrain segmental reports are shown below the graph of % normal MyoStrain (blue color codes normal deformation, green codes strain in the range between -17% and -10%, yellow codes strain less than -10%).

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Figure 8. A case 52-year female suffering from HER2 positive right breast cancer with a high risk of cardiotoxicity. Cardiac magnetic resonance (CMR) exams including Fast-SENC MyoStrain testing were performed at baseline and 6 follow-up intervals through 371 days after initiation of chemotherapy. The graph shows % normal MyoStrain (≤ -17%) in black with CMR LVEF in green and echocardiography LVEF in red. Upon administration of 270 mg/m^2 Epirubicin at 59 days follow-up, the patient exhibited clinical cardiotoxicity, with MyoStrain % normal LV myocardium worsened from 70% to 46%. Echocardiography LVEF (60 to 67%) and GLS (-19.7%) did not identify the cardiotoxic response. The dynamics of imaging parameters in response of titration of cardioprotective therapy is shown. MyoStrain segmental reports are shown below the graph of % normal MyoStrain (blue color codes normal deformation, green codes strain in the range between -17% and -10%, yellow codes strain less than -10%).

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Supplemental Figures

Supplemental Figure 1. Bull‘s eye of left ventricular (LV) global longitudinal strain (GLS) in a 62-year old man with a metastatic colorectal adenocarcinoma after 8 cycles of XELOX regimen (Capecitabine plus Oxaliplatin): GLS decreased from -14% before to -7,5% after chemotherapy.

Supplemental Figure 2. Bull‘s eye of LV longitudinal strain in a 63-year old female who underwent surgery, radiotherapy and chemotherapy for left breast cancer, which was finished 4 years ago. Recently severe LV systolic dysfunction was detected for the first time, along with the new onset of symptoms.

Supplemental Figure 3. Radiotherapy-induced cardiovascular disease: computed tomography images from a patient with effort dyspnea which manifested 24 years after mediastinal irradiation for Hodgkin lymphoma. **(A)** Severe calcification of ascending aorta and left anterior descending coronary artery. **(B)** Severe calcification of aortic and mitral valves. **(C)** Calcification of aortic valve leaflets in a zoomed short-axis view. **(D)** Fibro-calcified plaques with significant ostial stenosis of right coronary artery.

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Supplemental Videos

Supplemental Video 1A. A 62-year old man with a metastatic colorectal adenocarcinoma and a history of previous myocardial infarction. Echocardiographic four chamber view before initiation of chemotherapy showing mildly reduced LVEF (47%); measured global longitudinal strain (GLS) was -14%.

Supplemental Video 1B. Echocardiographic four chamber view after 8 cycles of XELOX regimen (Capecitabine plus Oxaliplatin) revealed deterioration of LV systolic function: EF 33%.

Supplemental Video 2A. A case of 66 years-old female with invasive breast ductal carcinoma (RH+HER2+) treated by the combination of doxorubicin, cyclophosphamide, paclitaxel, radiotherapy (35Gy+10) and Trastuzumab. Baseline measurement of segmental and global longitudinal strain in three apical planes and bull's eyes of peak systolic strain and time to peak systolic strain. Values are within normal range.

Supplemental Video 2B. Baseline 3D echocardiography and volumetric analysis of left ventricle and atrium: normal volumes and ejection fraction.

Supplemental Video 2C. Three months follow up measurement of segmental and global longitudinal strain in three apical planes and bull's eyes showing significant (19%) reduction of peak systolic strain and prolonged time to peak systolic strain.

Supplemental Video 2D. Six months follow up measurement of segmental and global longitudinal strain in three apical planes and bull's eyes showing substantial (10%) recovery of peak systolic strain and normalized time to peak systolic strain.

Supplemental Video 3A. A 63-year old female underwent surgery, radiotherapy and chemotherapy for left breast cancer, which was finished 4 years ago. Within 2 years after therapy completion LVEF was 50%, while after next 2 years dyspnea appeared and remarkable systolic dysfunction was revealed. Severe dilatation of LV and reduction of EF to 30%**,** apical 4 chamber view.

Supplemental Video 3B. Severe dilatation of LV and reduction of EF to 30%, apical 2 chamber view.

Supplemental Video 3C. Severe dilatation of LV and reduction of EF to 30%, short axis view.

Supplemental Video 4A. A case of 44 years-old male in NYHA III functional class. He had a history of Hodgkin lymphoma at the age of 19 treated with Doxorubicin, Bleomycin, Vinblastine, Dacarbazine (ABVD) and mediastinal radiation. 2D echocardiography with speckle tracking clearly showing severe systolic dysfunction: low left ventricular ejection fraction and global longitudinal strain (GLS).

Supplemental Video 4B. 3D echocardiography confirms remarkably low left ventricular ejection fraction before the treatment.

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Supplemental Video 4C. A striking improvement of segmental and global longitudinal strain after 6 months of medical heart failure treatment and cardiac rehabilitation.

Supplemental Video 5A. A 79-year old man admitted due to abdominal pain was diagnosed with advanced liver cancer. A heterogeneous lobular 6.0 x 5.0 mass with irregular edges and numerous cuttings, largely occupying the volume of right atrium, on two-dimensional echocardiographic 4 chamber view.

Supplemental Video 5B.

A heterogeneous lobular 6.0 x 5.0 mass with irregular edges and numerous cuttings, largely occupying the volume of right atrium, on three dimensional echocardiographic view.

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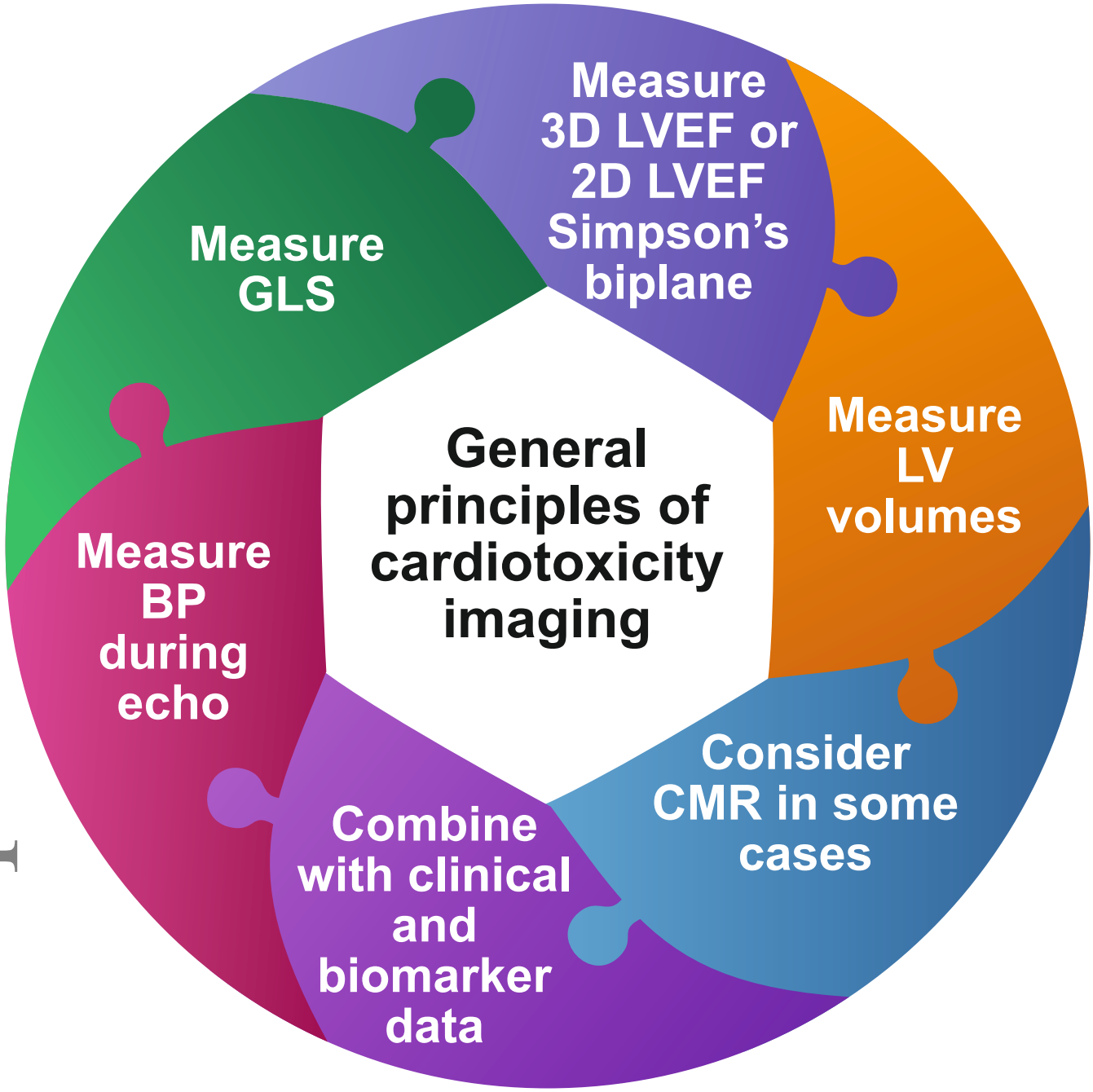

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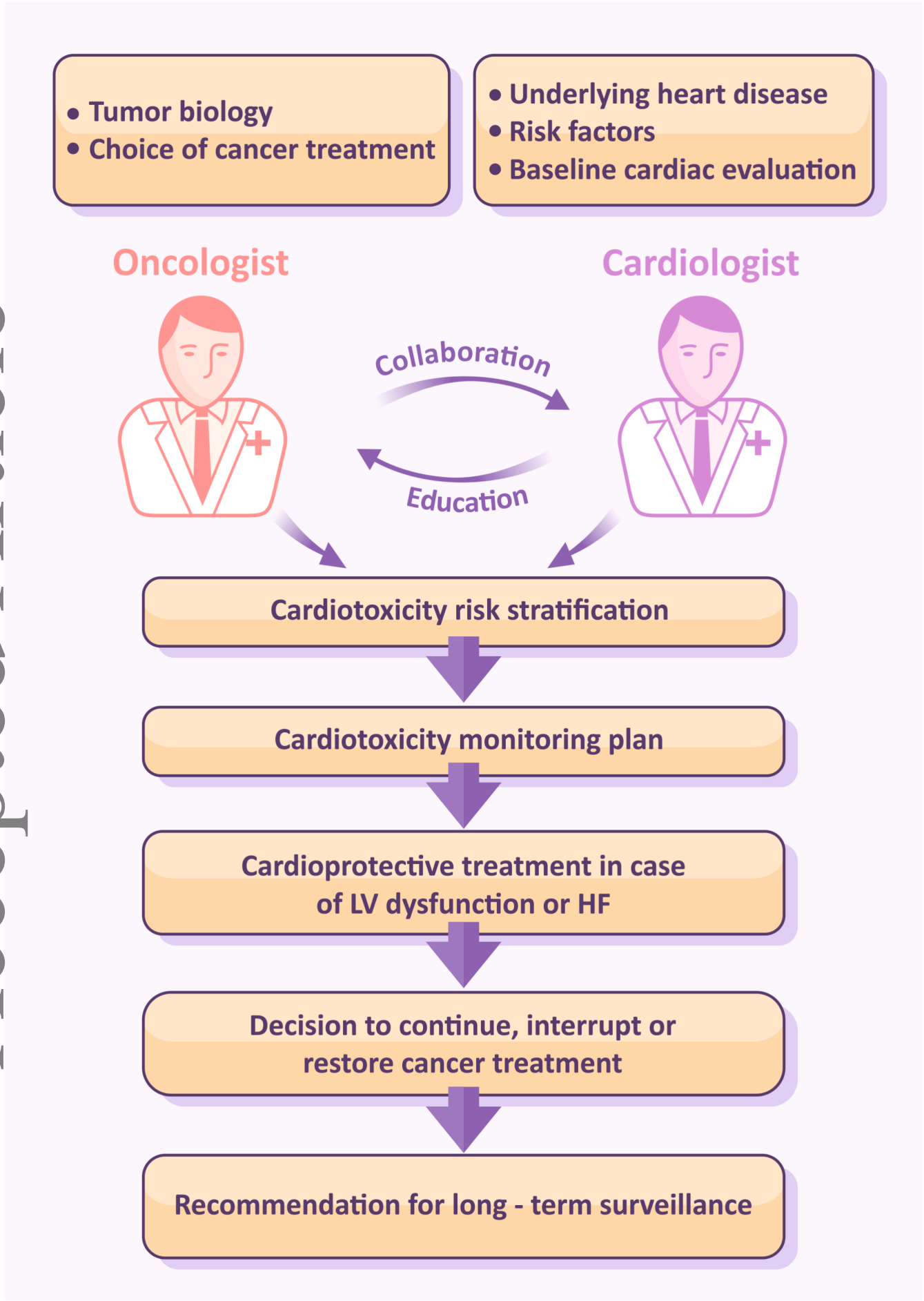

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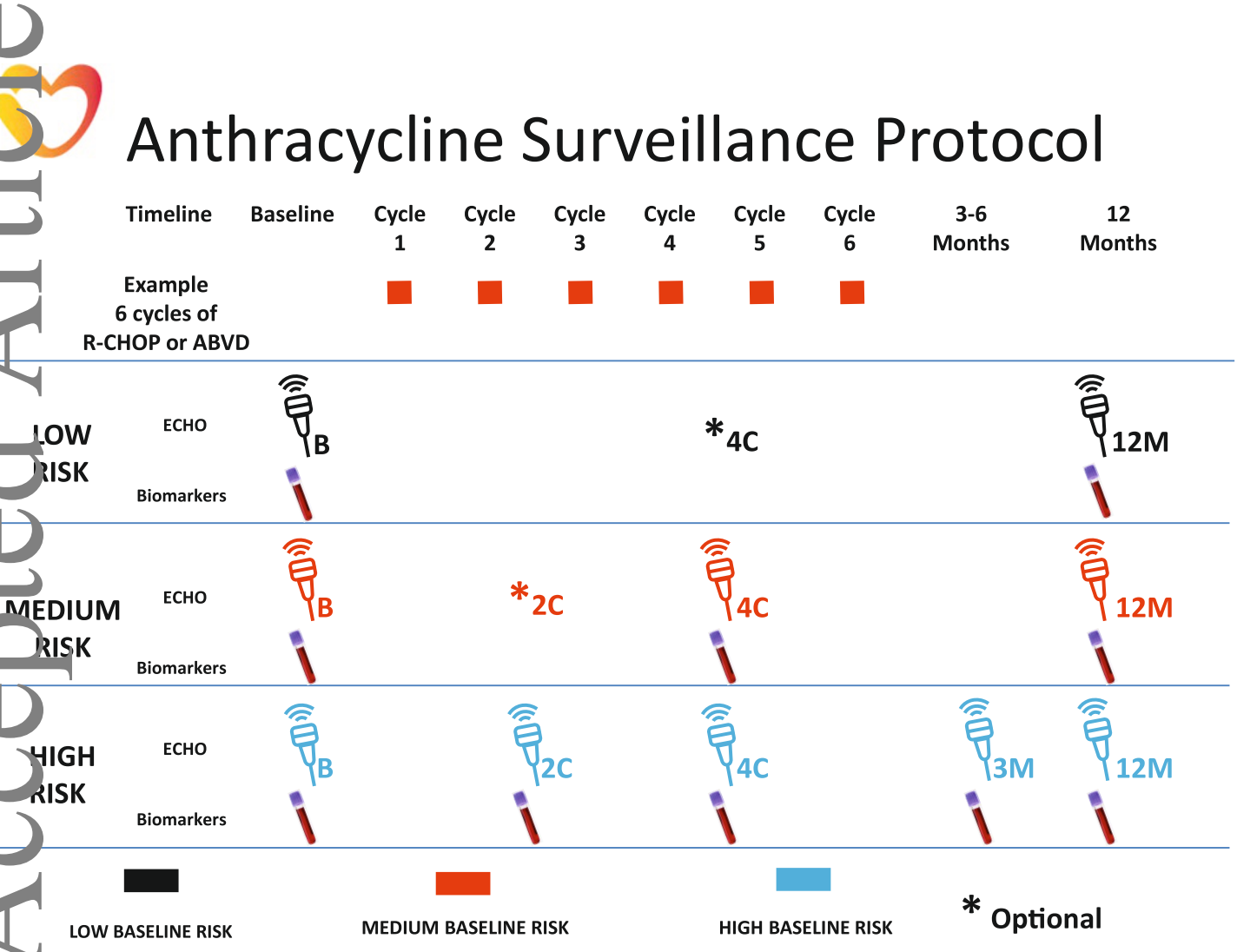

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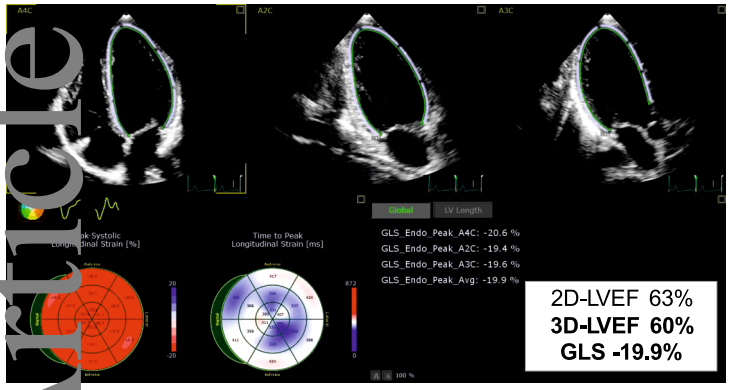

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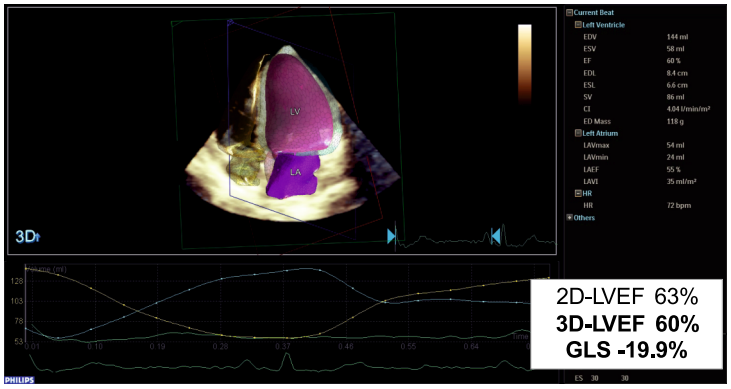

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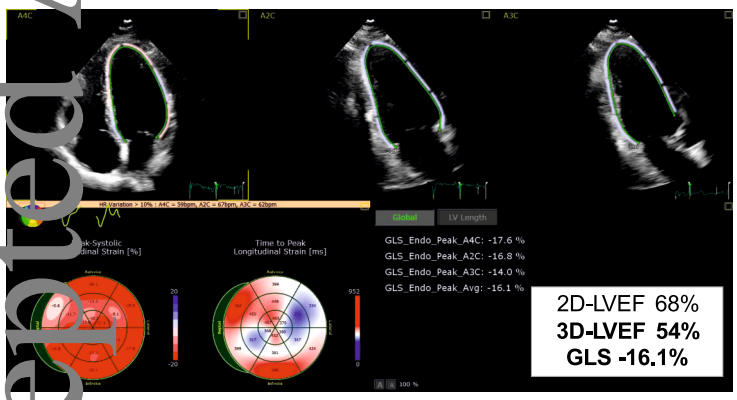

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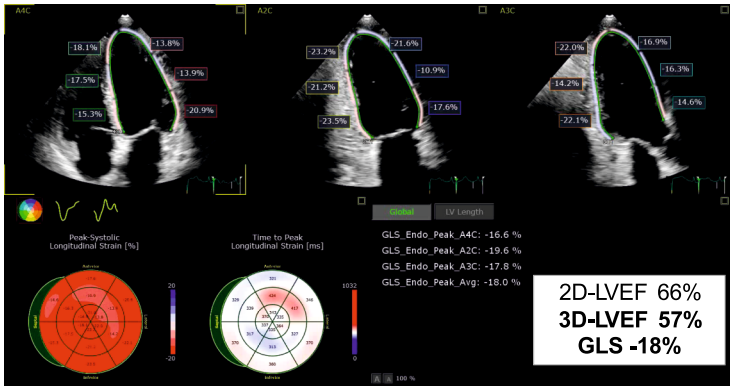

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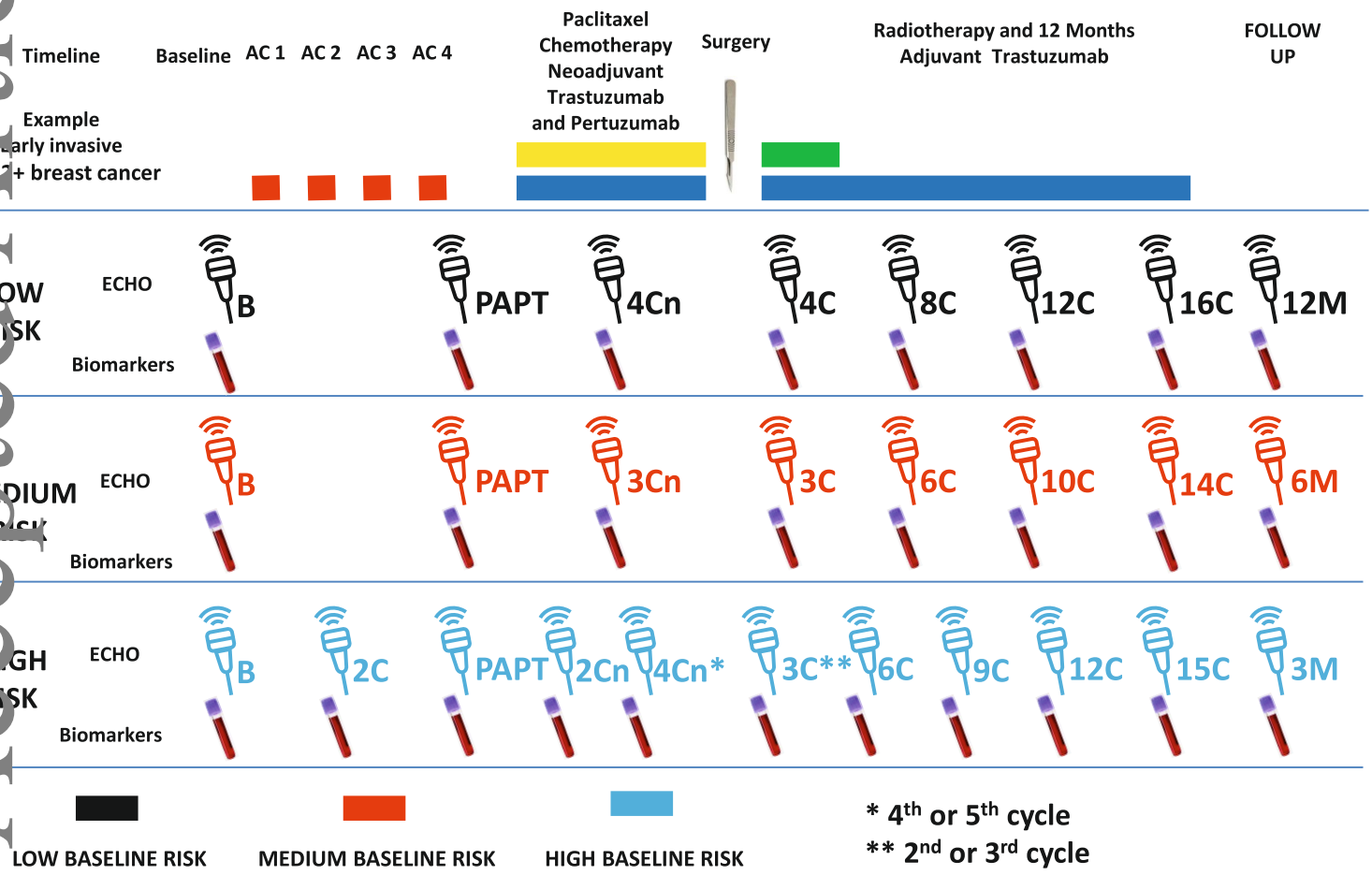

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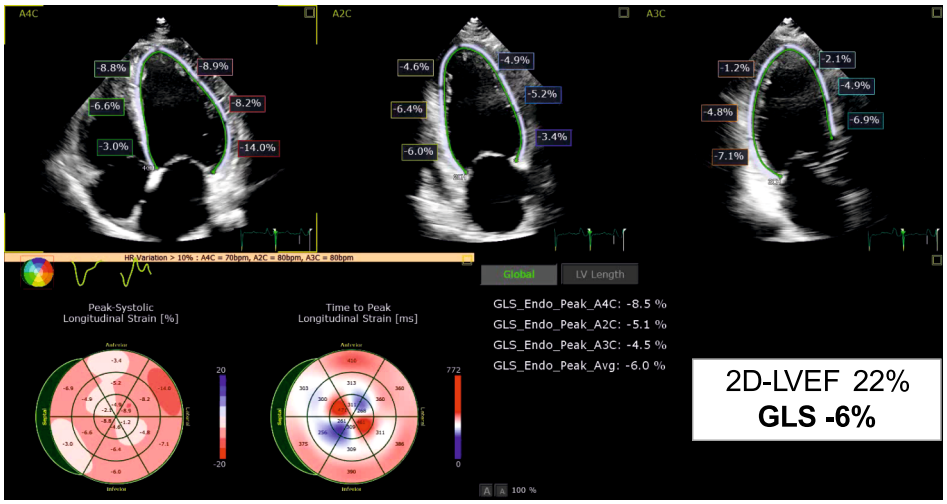

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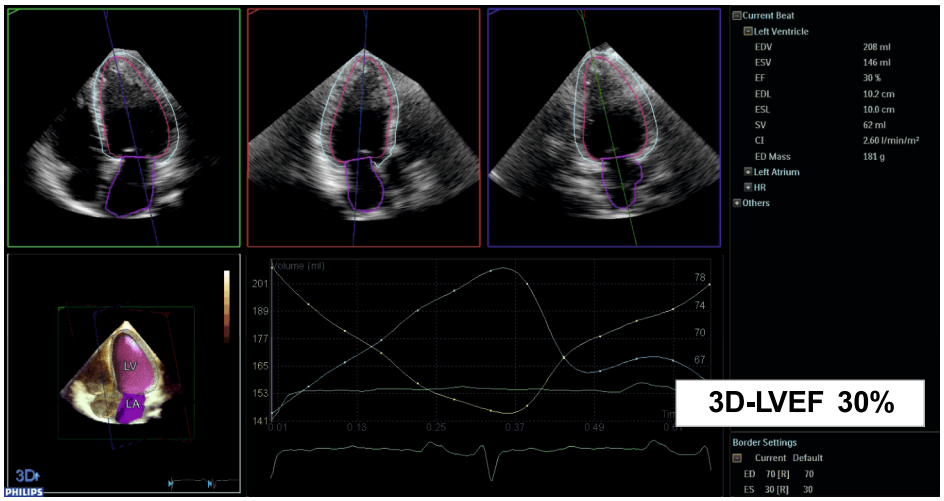

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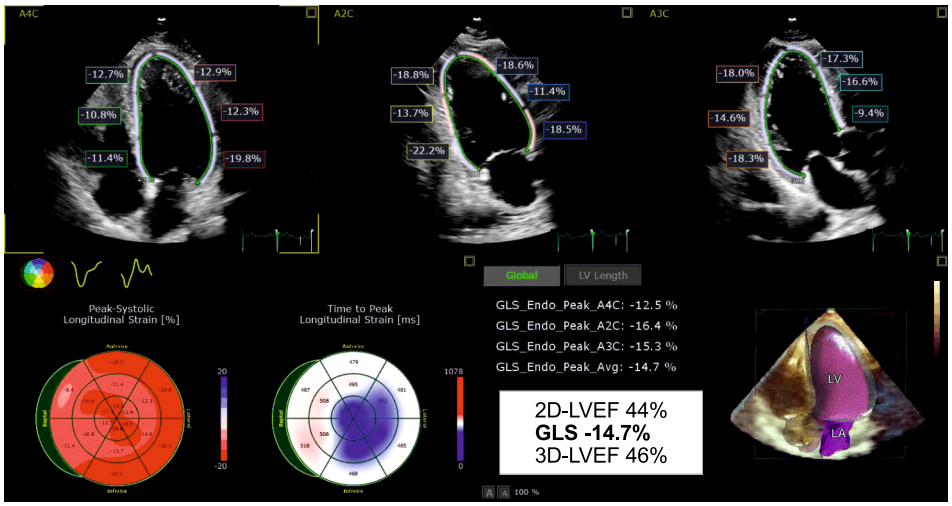

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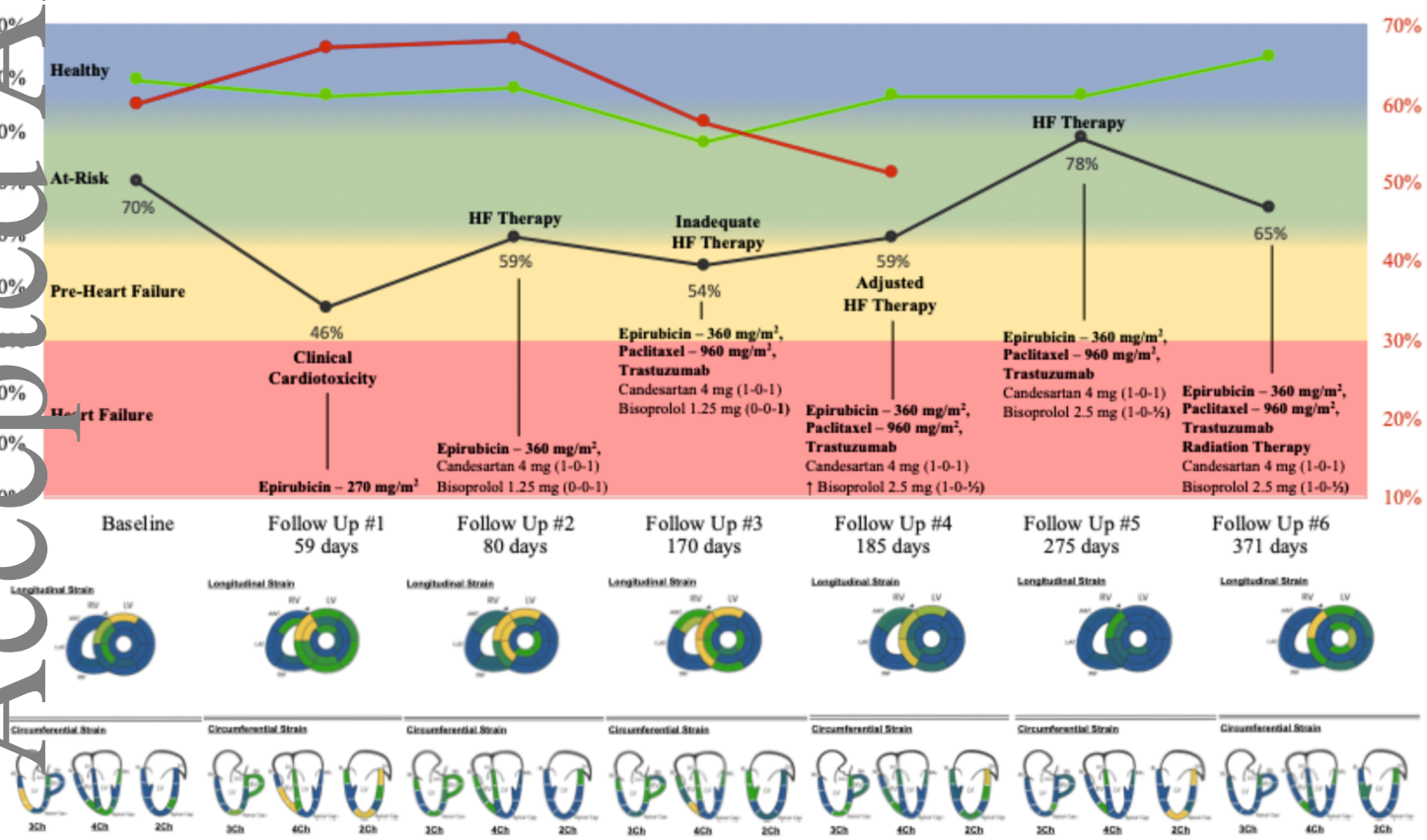

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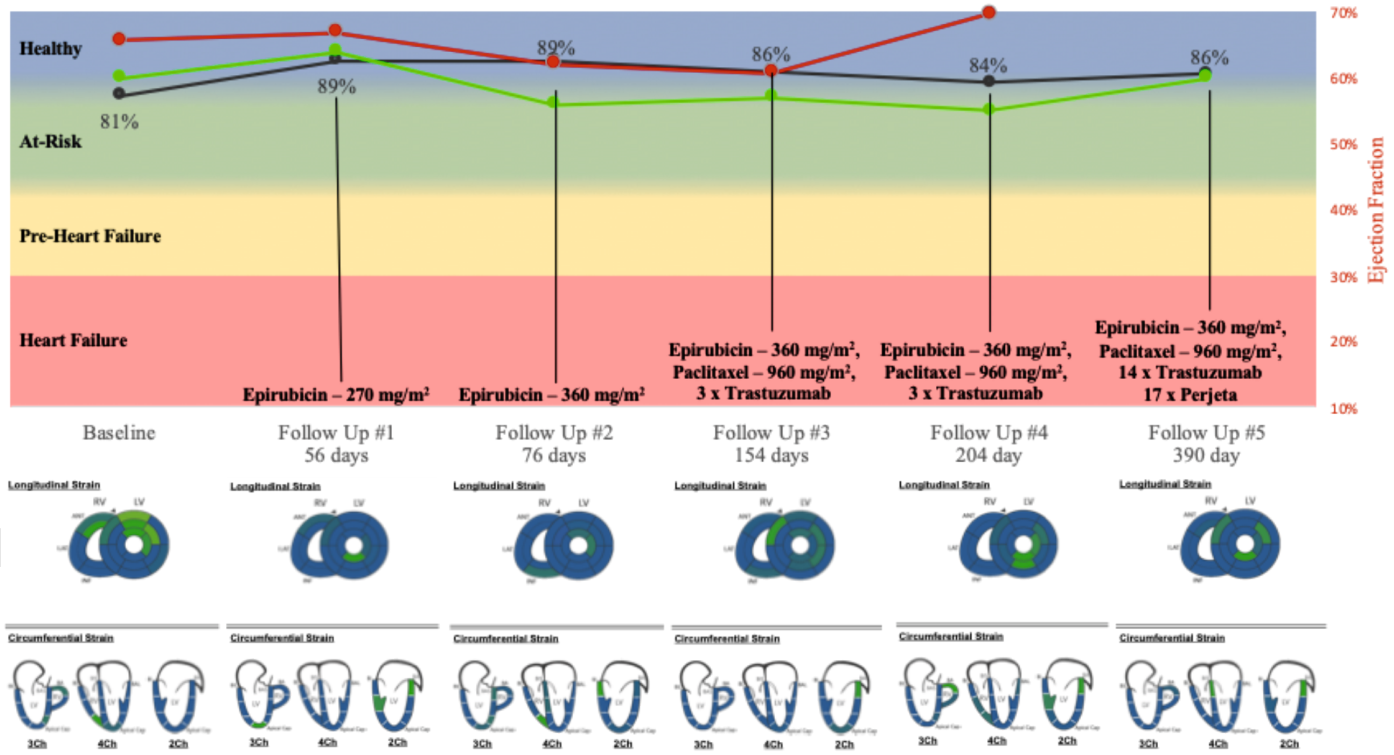

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