MITIGATION OF TREATMENT RELATED CARDIOTOXICITY IN PATIENTS WITH THORACIC MALIGNANCIES

Abstract

Thoracic malignancies have always been of great concern. Surgery, chemotherapy and mediastinal radiation are an integral component of treatment of a variety of thoracic malignancies. Improvement in therapeutics and technology has increased the longevity of these patients and hence its not uncommon to witness long term survivors. This has changed the ultimate goal of treatment which is no more just cure rather the focus is now cure along with quality of life. Heart being the central thoracic structure bears the major brunt of adverse effects following mediastinal radiation and chemotherapy. More research into the underlying pathophysiology is required to improve and implement the screening protocols for identifying preclinical cardio toxicity and allow for earlier interventions. Although significant improvement in the techniques of radiation and judicious use of cardio toxic drugs have reduced the incidence of these cardiac events. But still treatment induced cardio toxicity remains potentially significant for many patients with thoracic cancers. A variety of futuristic trends are implemented like improved knowledge about radiation doses limitations to cardiac substructures allows for better personalization of radiation in the times to come. Better application of cardiac contouring atlases in routine clinics and case management is required. Adapting to the protocols of reduced radiation field and dose together with vigorous attempts of using breath hold technique, prone positioning and the latest techniques of radiation along with aggressive cardiovascular risk modification can help in further reducing the incidence of radiation induced cardiac disease.

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I. INTRODUCTION

Advancements in clinical sciences and imaging technologies have lead to increase in the detection of cancer at early stages. Patients can therefore benefit with early introduction of anticancer treatment and this has increased the longevity in majority of the sub sites. But owing to exposure to a plethora of new therapies including drugs and radiation,the long term toxicities have become more evident.

Radiation therapy is an essential component of treatment strategies for majority of thoracic malignancies including carcinoma breast,carcinoma lung,carcinoma esophagus,lymphoma etc wherein radiation can be used in definitive, adjuvant, neoadjuvant or palliative setting. Apart from the tumor,the adjacent organs are also exposed to the effects of radiation and chemotherapy. Anthracycline induced cardiotoxicity poses a significant clinical challenge in the management of cancer patients. The heart suffers the major brunt of adverse effects which ranges from pericarditis, pericardial effusion etc which are common acute side effects appearing within weeks following treatment. Some adverse effects may come to light months to years after exposure to therapeutic radiation (as late as 20 years or more) and may be evident in the form of symptomatic coronary artery disease (CAD), valvular heart disease or heart failure.

Congestive heart failure is the most common complication due to anthracycline induced toxicity because of its effect on morbidity and mortality[1]. A variety of drugs are available for the treatment of heart failure such as ACE(angiotensin converting enzyme) inhibitors, Angiotensin receptor blockers, beta blockers, aldosterone antagonists , diuretics etc. ARNi angiotensin receptor/neprilysin inhibitor is a new addition to this armamentarium made up of an ARB (angiotensin II receptor blocker) and a neprilysin inhibitor. Sacubitril/valsartan is the first agent to be approved in this new class of drugs called angiotensin receptor neprilysin inhibitor (ARNi).

II. PATHOPHYSIOLOGY

Radiation induces generation of free radicals and pro inflammatory cytokines which react with cellular DNA causing disruption of the strand thereby preventing replication and protein synthesis. Although cardiomyocytes are considered to be relatively resistant to radiation but still there is 4-16 percent risk of major cardiac events with each increasing Gray of mean heart dose.Radiation causes endothelial dysfunction of the microvasculature leading to thrombosis and small vessel disease of the myocardium leading to structural changes of the heart as a sequelae of pericardial inflammation,fibrosis of myocardium and electrical conduction system majorly. The inflammation can lead to pericarditis or pericardial effusion. The proinflammatory cytokines can cause intimal reaction and fibrin deposition accelerating the progression of coronary artery disease[2].Chronic fibrosis of the pericardium can lead to constrictive pericarditis. Diffuse infiltrative fibrosis in the myocardium can impair the ability of the ventricles to relax resulting in a diastolic failure. The conduction system of the heart can also be affected and appear as arrythmias later in life. The deleterious effects of radiation can be seen even years after wherein the valvular endothelium can be damaged or fibrosed leading to backflow or stenosis[3].

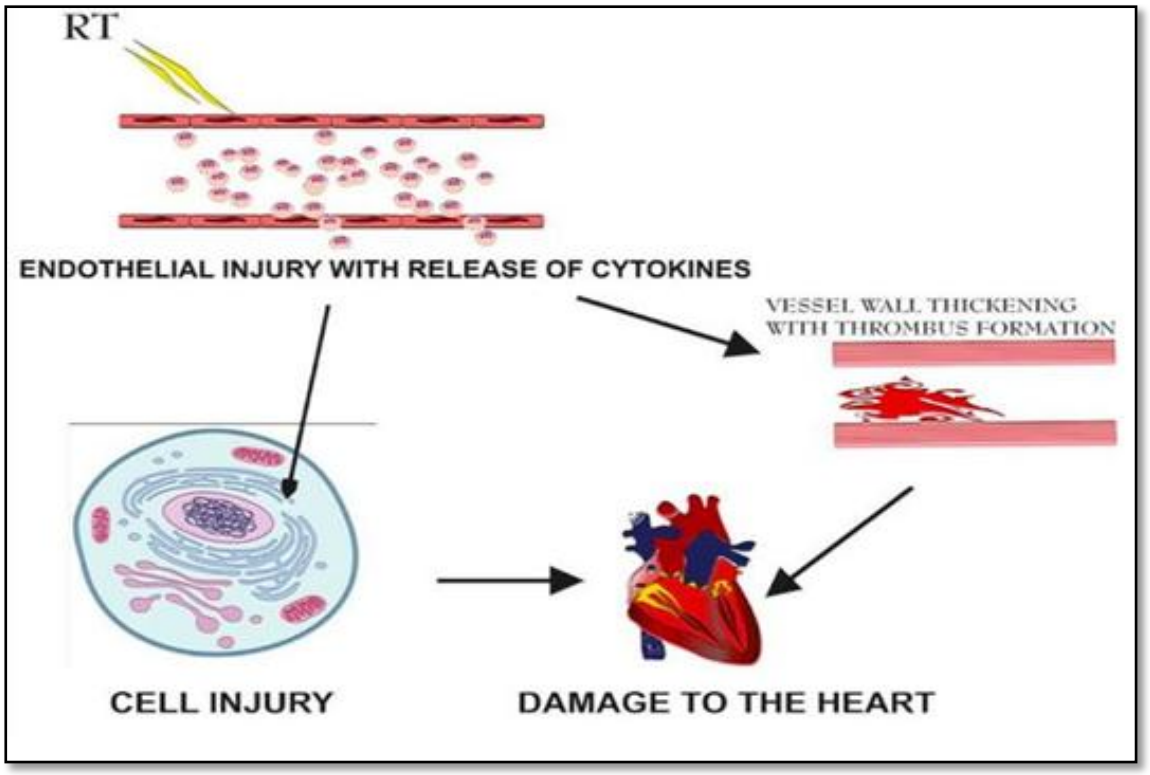

Illustration 1: Diagram showing effect of radiation on the vessels

Anthracycline induced cardiotoxicity occurs as a result of activation of vascular cells including platelets, monocytes, and endothelial cells which are then exposed to surface phosphatidylserine (PS), this leads to activation of pre-existing tissue factor (TF) on monocytes and endothelial cells, and finally the release of TF-bearing extracellular vesicles (EV)[4] occurs.

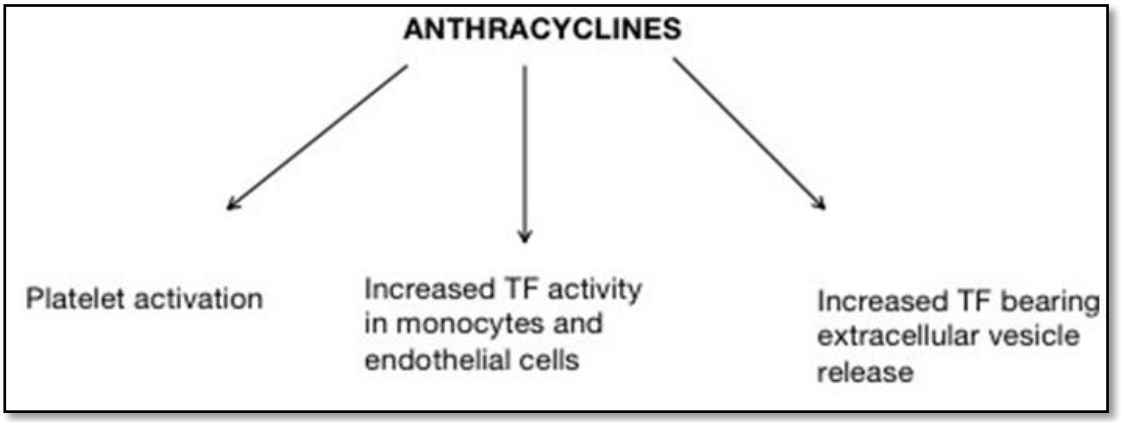

Illustration 2: Flowchart showing effect of anthracyclines on the vessels

III. EFFECTS OF RADIATION ON HUMAN HEART

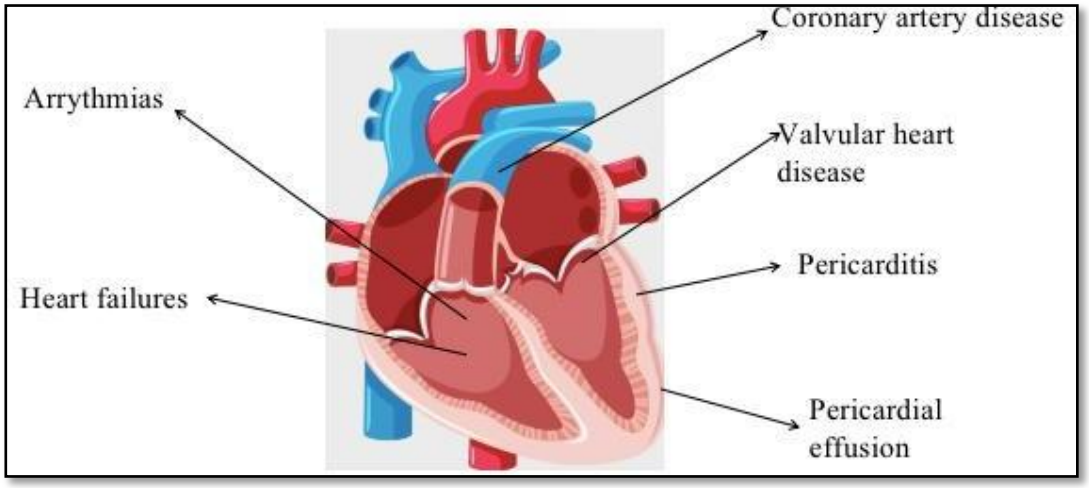

Illustration 3: Diagram showing effect of radiation on heart

IV. EFFECTS OF ANTHRACYCLINES ON HEART

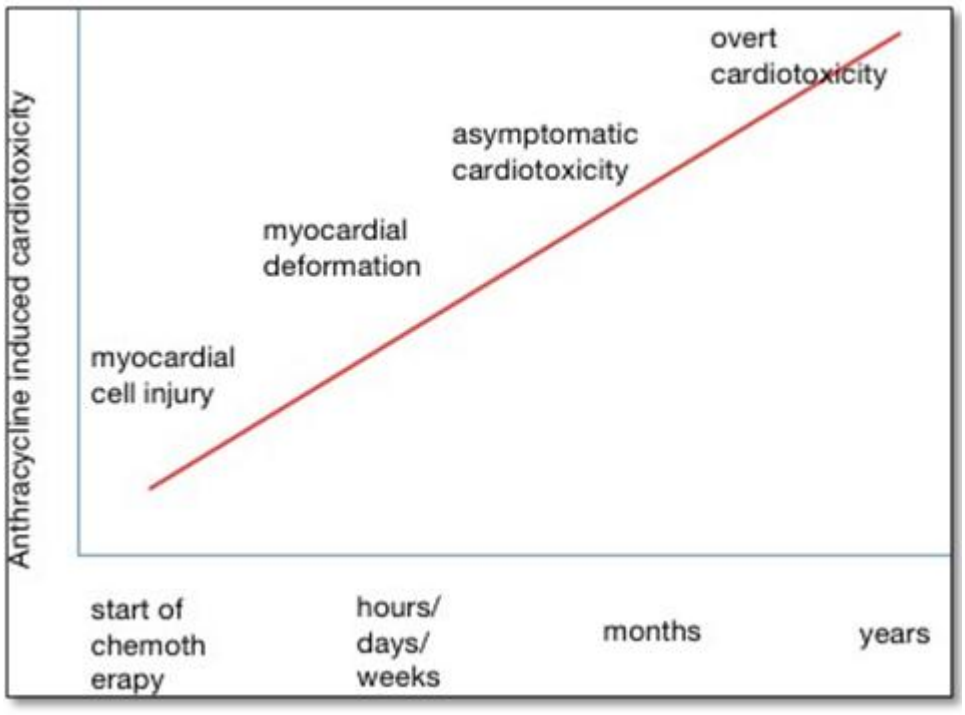

Illustration 4: Graph showing effect of time duration of Anthracyclines on heart

V. PREVENTION OF CARDIOTOXICITY SECONDARY TO THORACIC RADIATION OR ANTHRACYCLINE BASED CHEMOTHERAPY

1. **Risk Factor Adjustment:** adequate baseline screening of patients for traditional risk factors (smoking, diabetes and hypertension) and imaging risk factors (coronary artery calcifications) is a predictor of future cardiovascular events in patients undergoing treatment for thoracic malignancies. Preexistence of any cardiovascular risk factor increases the risk of acquiring a major coronary event. A history of ischemic heart disease carries almost a 6 fold higher risk of a future cardiac event in women treated for carcinoma breast. This risk is higher in the first 10 years after cancer diagnosis [1] . Smoking combined with radiation triples the risk of myocardial infarction compared to non smoker patients treated for breast cancer. High cholesterol has been studied as a confounding factor for development of coronary atherosclerosis in Hodgkin lymphoma survivors. The effects of preexisting cardiovascular risk factors have been equally detrimental in patients with advanced carcinoma lung undergoing radiation.This risk increases with the use of anthracycline based chemotherapy along,before or after mediastinal radiation. Hence smoking cessation,adequate blood sugar control,lowering of blood pressure and cholesterol are the key determinants of the cardiovascular adverse effects following the use of anthracyclines and mediastinal radiation.

2. **Intensity Modulation and On Couch Imaging:** owing to improvements in treatment technology, the radiation exposure to the adjacent structures surrounding the target has decreased over time. In the historic era of 2 dimensional radiotherapy,the bony landmarks were used to define borders of the radiation field,hence a documentation of the doses received by the underlying structures was not possible. Overtime the treatment has evolved from 2 dimensions to 3 dimension with time now being identified as the 4^{th} dimension which tracks the motion of the tumor. Advancements in radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) may reduce the risk of cardiac toxicity as a result of the sharp dose gradient limiting the volume of the heart irradiated to a high dose. Image-guided radiotherapy (IGRT) is a further refinement of IMRT delivery with daily imaging, which may further reduce excessive cardiac irradiation. The superiority of IMRT over 3D-CRT (3 dimensional conformal radiotherapy) has been extensively studied in terms of dose reduction to myocardium in patients with left mean heart volume receiving more than 30 Gy were 2.6 and 16.4% for IMRT and 3D-CRT, respectively [6]. The use of image guidance along with IMRT gives the possibility of reduction of set up margins allowing for better sparing of normal tissues and at the same time promoting tumor dose escalation.

3. **Respiratory Gating:** In an attempt to reduce the dose to underlying heart and lung in patients receiving mediastinal radiation, deep inspiratory breath hold (DIBH) technique has been extensively studied. This technique reduces cardiac exposure by lung expansion physically displacing the heart out of the radiation field. Compared with free breathing, DIBH resulted in a significant reduction in heart V30 (7.1 vs. 2.4%, $P < 0.0001$), mean heart dose (6.9 vs. 3.9 Gy, $P < 0.001$) [7]. In a cohort of breast cancer patients undergoing radiation including regional nodes, DIBH allowed a greater reduction in mean heart dose and LAD (left anterior descending artery) dose compared to free breathing [8]. Tracking of tumor movement with breathing has been successfully exploited for reducing the radiation related cardiac events.ABC (active breathing

control) causes moderate to deep inspiratory breath hold, other technique uses respiratory gating with chest wall sensors to trigger delivery of radiation therapy based on respiratory expansion of the thorax can be used.Cardiac mortality can reduce by 4.7% by using Breath hold and respiratory gating techniques compared with free breathing techniques in patients with left sided tumors, with a median cardiac mortality normal tissue complication probability (NTCP) of 0.1% [9,10] .DIBH combined with IGRT can further reduce the radiation dose to the heart with greater advantage seen in patients with left sided breast cancer. In a study in patients with left-sided breast cancer treated using IGRT,a significant reduction was seen in the percentage of volume of left ventricle irradiation 28% vs 71% for DIBH and free breathing respectively [11].

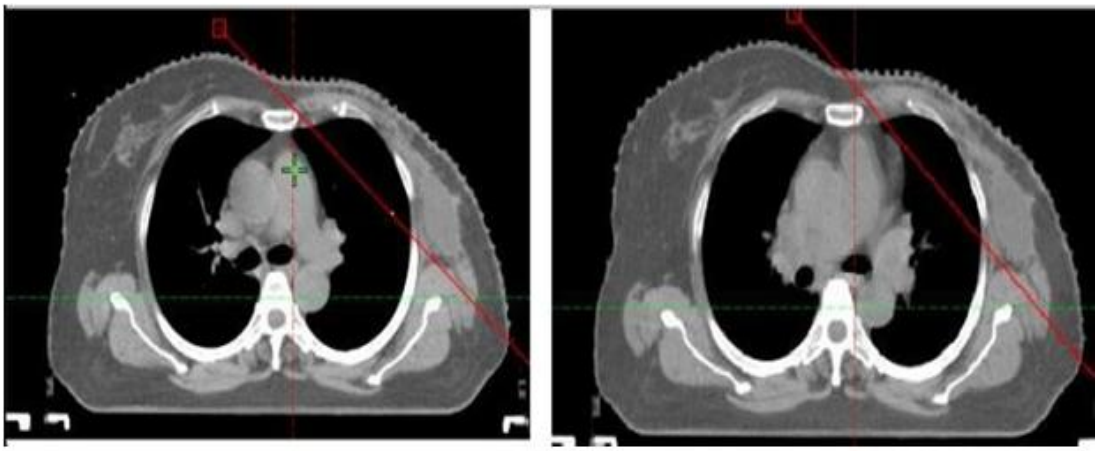

Figure1: Axial section of CT thorax showing the effect of breath hold

4. **Treatment in Prone Position:** This technique was developed in an attempt to decrease the dose to the underlying structures in patients treated for carcinoma breast. It was found to be of use in patients with large, pendulous breast. It allows the breast to fall away from the chest wall thereby increasing the distance between the heart and the breast tissue being irradiated [12]. An analysis by the New York University on 100 patients (53 with left-sided cancers) comparing prone versus supine treatment found that prone positioning reduced the in-field heart volume by 12 cc in 90% of patients [13] .Mixed data is available regarding use of prone positioning for reducing cardiac dose in patients undergoing breast irradiation majorly due to lack of appropriate reproducibility. In comparison to the supine position,the superior and lateral aspects of the heart typically moveanteriorly during the prone setup .This may have negative consequences in situations in which the target tissues receiving high dose of radiation include the chest wall or deep breast.More long term follow up is needed with cardiac outcomes being evaluated as specific end points.

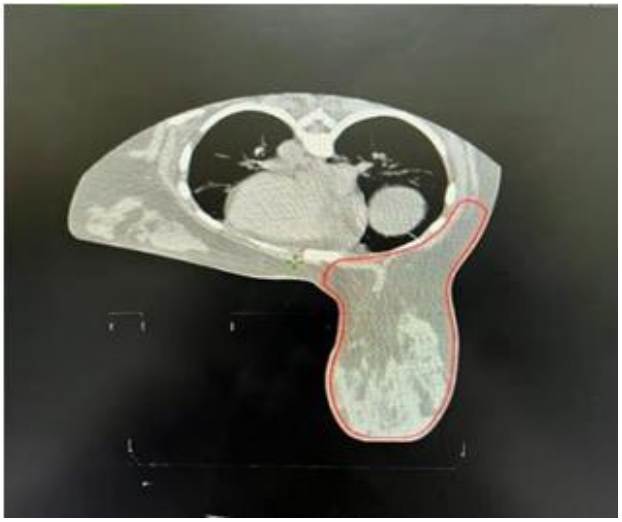

Figure 2: depiction of prone breast positioning for sparing the heart

5. **Proton Beam Therapy:** The beam characteristics of the proton particle allows for a sharp dose fall off beyond the brag peak leading to a dose reduction to critical structures and hence reduction in the acute and late toxicities. Although it has been majorly utilised in pediatric malignancies,skull base tumors, orbital tumors and reirradiation, is now being employed in other subsites including thoracic malignancies. Use of proton beam therapy (PBT) has been compared with IMRT in treating patients with carcinoma breast and there has been a significant reduction in the heart doses [14]. Single field PBT is now being replaced by intensity modulated proton therapy (IMPT) and has been found to reduce V20Gy and V5Gy of the heart [15]. Despite its promising results the use of PBT is limited due its high cost concerns [16].Hence in the light of limited data and limited cost effectiveness, proton beam therapy is not one of the choicest modalities for reducing cardiac dose in patients undergoing mediastinal irradiation.

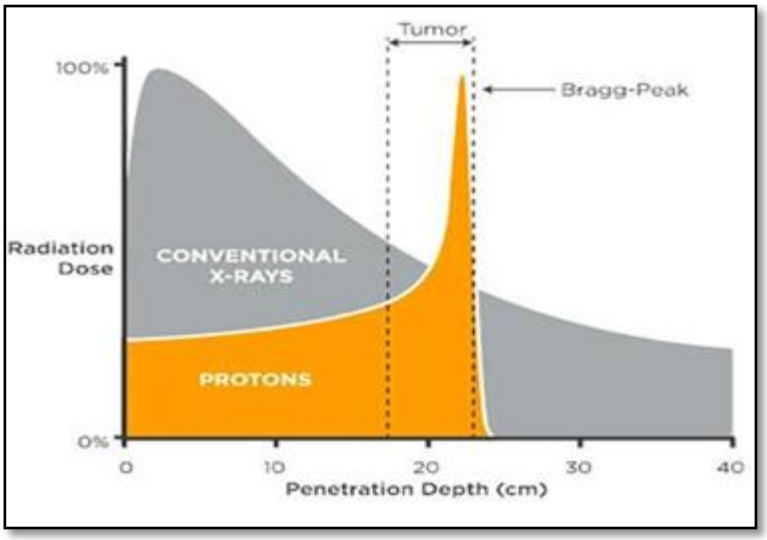

Figure 3: Showing Bragg Peak of a Proton Beam

6. **Partial Breast Irradiation:** This technique of irradiating just the lumpectomy cavity with a margin around is being increasingly used in patients with early breast cancer. It can be used as an alternative method to reduce cardiac doses since by reducing the volume of tissue being irradiated,the distance between heart and target volume is increased. The only concern is the effect of high dose per fraction on the cardiac tissues which have lower alpha/ beta [17]. But a few studies addressing this concern have shown no negative effect on heart [18.] APBI (accelerated partial breast irradiation) is one of the types of partial breast irradiation.APBI can be done with either brachytherapy (interstitial or balloon based) or with external beam therapy . APBI is used in patients with early stage breast cancer who have a long survival post treatment hence every measure should be taken to restore a good quality of life to these patients. A plethora of dosimetric studies are available on the use of interstitial brachytherapy for APBI. There is a significant reduction not only in the volumes of the lung and heart receiving low doses of radiation (V5 and V10Gy)but also in the maximum dose received by small portions of heart (D 0.1cc). Taking into account the simplicity of using balloon based cathethers ,the interstitial brachytherapy is replaced by balloon brachytherapy during the last decade [19]. But the benefit of dose reduction to underlying structures is still maintained.

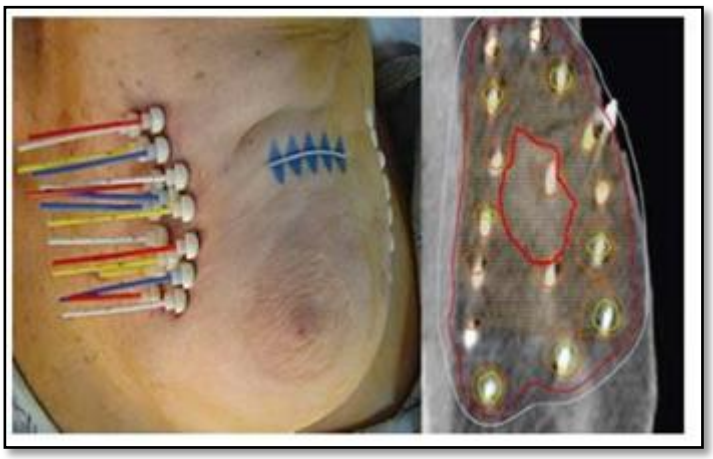

Figure 4: Depiction of APBI by multicatheter brachytherapy (photo credits- Col Dr.Ashok Kumar)

7. **Cardiac Substructure Identification:** The risk of cardiac events is related to the dose and volume of the substructures irradiated. There is a difference in the radiation tolerance of the various cardiac substructures. For proper delineation of these substructures ,the University of Michigan cardiac atlas was designed [20]. Anterior myocardial territory (AMT) has been identified to bear the major brunt of dose in mediastinal irradiation. AMT includes the myocardium from the anterior surface of heart to 1cm from the posterior surface,the major epicardial coronary arteries at the anterior surface such as LAD, left circumflex and left and right main coronary arteries. It is necessary to pay attention to prevent overdosing of these structures in the anterior part of the heart. Strict dose constraints to these structures might be useful in reducing the cardiac events further [21].

VI. PRIMARY PREVENTION OF ANTHRACYCLINE INDUCED

Cardiotoxicity: Use of liposome encapsulation which modifies pharmacokinetics and tissue distribution without compromising antitumor efficacy or use of less cardiotoxic derivatives like epirubicin or idarubicin at the outset modifies or reduces the chances of anthracycline induced cardiotoxicity. Avoiding the use of anthracyclines as a bolus dose is a great attempt at the primary level that causes less damage to the heart. Hence the use of divided doses is advocated. Use of dexrazoxane also significantly reduces the cardiotoxicity caused by anthracyclines[22]. Although there is a spectrum of cardiac complications caused by anthracyclines but a significant attention has been given to Congestive heart failure due to its effect on morbidity and mortality. A variety of drugs are available for the treatment of heart failure such as ACE(angiotensin converting enzyme) inhibitors, Angiotensin receptor blockers, beta blockers, aldosterone antagonists , diuretics etc. ARNi angiotensin receptor/neprilysin inhibitor is a new addition to this armamentarium made up of an ARB (angiotensin II receptor blocker) and a neprilysin inhibitor. Sacubitril/valsartan is the first agent to be approved in this new class of drugs called angiotensin receptor neprilysin inhibitor (ARNi).

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