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RADIATION INDUCED VALVULAR CHANGES AND ITS CORRELATION WITH OTHER 2D-ECHO AND ECG FINDINGS IN PATIENTS OF THORACIC CANCERS - A REVIEW OF LITERATURE

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ABSTRACT- Valvular Injury post Radiotherapy is the result of acute asceptic inflammation and myocardial damage seen less than 6 months after radiation and can remain as chronic cardiovascular complication. Associated pericarditis can induce ST Segment changes in ECG .Bradycardia has correlation with Global hypokinesia of left ventricle while Ejection fraction may remain unaffected. Here we have reviewed relevant literature from Pub Med ,Google Scholar and Scopus libraries for study of changes in heart post radiotherapy of Thoracic Malignancies.

DATA AVAILIBILITY STATEMENT- It is not applicable to this article as no new data was created in this study. The following is review article to enhance one's knowledge in the field of radiation induced heart disease.

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KEYWORDS-Radiation, valvular, ECG, ECHO, Thoracic**.**

INTRODUCTION- RIHD (Radiation induced heart disease) includes a spectrum of cardiovascular complications ranging from subclinical asymptomatic microscopic changes in heart to overt heart failure. The most common cardiac complication to radiotherapy is pericardial (ranging from asymptomatic pericardial effusion to constrictive pericarditis), and conduction abnormalities are the least common.

Pathogenesis **-** RIHD can be acute or chronic effects on heart. Radiobiologically heart acts both as a parallel and series organ. For example, injury to a small part of myocardium may be asymptomatic and goes unnoticed while injury to a small segment of coronary arteries or the conducting system may be dangerous and life threatening.

Presentation of acute RIHD may range from asymptomatic involvement to acute pericarditis. The acute phase is mediated by tumor necrosis factor (TNF), and interleukins (IL) IL-1, 6, and 8 further leading to neutrophil infiltration. The acute effects are usually self-limiting and respond well to conservative management.

Pericarditis **-**The clinical process of pericarditis can be divided into 4 stages including acute and chronic pericarditis, fibrinous pericarditis , and the final evolution, constrictive pericarditis.The most frequent manifestation of acute stage is exudative pericarditis Its occurrence is mainly related to damage of capillary endothelial cells and lymphatic stenosis or occlusion.When the radiation dose is increased by 10 Gy, the morbidity increases five times[23].

Valvular heart disease **-** Myocardial ischemia and hypoxia caused by myocardial fibrosis and coronary diseases are the basic causes of valve function injury. Mitral regurgitation and aortic regurgitation overall are the most common defects. When stenosis occurs, aortic regurgitation is frequently involved[36]. Conduction system abnormality Conduction system abnormality caused by RT usually manifests as atrioventricular block, pathological sinus node syndrome, QTc prolongation, supraventricular arrhythmia and ventricular tachycardia[26] .

Cardiomyopathy -The clinical symptoms of myocardial injury caused by RT are quite late, mainly manifested as myocardial fibrosis.Myocardial injury is common in patients who have received an high dose of radiation (>60 Gy). Patients who have received high dose of radiotherapy are prone to restrictive myocardial injury, and who have received chemoradiotherapy are prone to diastolic myocardial injury[24].

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

Coronary artery disease (CAD)- The injury of coronary artery induced by radiation is consistent with coronary atherosclerosis due to additional factors. The initial trigger was still endothelial cell injury the infiltration of monocytes into the intima, inducing low-density lipoprotein deposition and the formation of fatty streaks[25].

TABLE 1 - *CLINICAL FEATURES AND TREATMENT OPTIONS IN RADIATION INDUCED HEART DISEASE* **[22]**

SYNDROMES	CLINICAL FEATURES	INVESTIGATIONS	TREATMENT
ACUTE PERICARDITIS	FEVER,CHEST PAIN,PERICARDIAL RUB	ECG,2DECHO,	SELF LIMITING,NSAIDS,DIURETICS
CHRONIC PERICARDITIS	DYSPNOEA, ELEVATED JVP	ECG,2D ECHO,CXR,CECT CHEST	LOOP DIURETICS , PERICARDIOCENTESIS
CARDIOMYOPATHY, CHF	DYSPNOEA,FATIGUE,PULMONARY EDEMA	ECG,2D ECHO	LOOP DIURETICS,ACE INHIBITORS,VASODILATORS
CORONARY ARTERY DISEASE	CHEST PAIN ,HEAVINESS,DYSPNOEA	ECG,2DECHO,ANGIOGRAPHY	ANTI-PLATELETS,ANTI-ARRHYTHMIC DRUGS,PACEMAKER
CONDUCTION ABNORMALITIES	PALPITATIONS,DIZZINESS,SHORTNESS,OF BREATH	ECG,2DECHO	ANTIARRHYTHMIC DRUGS,ANTIPLATLET DRUGS,PACEMAKER ,CATHETER ABLATION

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

MitraClip for radiotherapy- Owing to mediastinal and cardiac damage burden, the surgical treatment of radiotherapy-related mitral regurgitation (MR) may be associated with high operative risk or might even contraindicated.

Scarfo' et al.[2] Showed that Following MitraClip MR improved (residual MR ≤2+) without significant mitral valve stenosis (planimetric area 2.83 ± 0.8 cm2, mean gradient 4.6 ± 1.8 mm Hg). All patients completed a 6-month follow-up, while 14 of 15 patients achieved a longer follow-up, ranging from 12 to 72 months (median 24 months, IQR 42 months).

CARDIOVASCULAR PROTECTIVE EFFECT OF ESTROGEN -

Radiation can cause coronary endothelial injury leading to a pro-inflammatory state, the rupture of vessel walls, platelet aggregation, thrombosis and the replacement of damaged intima by myofibroblasts, resulting in vessel stenosis and atherosclerosis. Women with a history of breast cancer receiving radiotherapy show a relative 7.4% increase in the risk of cardiovascular events with each gray of radiation exposure. Furthermore, for reasons that are unclear, women treated with mantle or mediastinal radiation for Hodgkin lymphoma have a significantly higher cardiovascular event rate and mortality compared to those in men, highlighting the need for increased surveillance. Reduced cardiovascular-specific survival has also been reported in women treated with radiation for cervical and uterine cancers [18].

Radiation-associated cardiotoxicity appears to be delayed—typically 10 to 30 years following treatment. In patients with prior Hodgkin's lymphoma having undergone radiation therapy, the median time from diagnosis of malignancy to cardiac complications was 19 years. The risk of inducible ischemia on myocardial perfusion scans increases from 5% at 10 years postradiation, to 20% at 20 years postradiation.Finally, for reasons that are still unclear, women tend to have more cardiovascular events and mortality compared with men with radiation-induced cardiovascular disease.However, these findings could be explained by the fact that at least half of the women in these studies were postmenopausal and therefore lacked the cardiovascular protective effect of estrogen[19].

REVIEW OF LITERATURE-

Cardiovascular disease is now the most common nonmalignancy cause of death in radiation-treated cancer survivors, most often occurring decades after treatment. The

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

spectrum of radiation-induced cardiac disease is broad, potentially involving any component of the heart. The relative risk of coronary artery disease, congestive heart failure, valvular heart disease, pericardial disease, conduction abnormalities, and sudden cardiac death is particularly increased. Over the years contemporary techniques have been introduced to reduce cardiac morbidity and mortality in radiation-treated cancer survivors; however, the long-term effects on the heart still remain unclear, mandating longer follow-up. Awareness and early identification of potential cardiac complications is crucial in cancer survivors, with the management often being quite complex [4].

Priya et al. [1] found that after 6 months of radiotherapy, 8 out of 40 patients of esophageal cancer post radiotherapy showed global hypokinesia of left ventricle. Trivial Mitral regurgitation was seen in 9 out of 40 patients.

Zhang et al. [28] in their study found similar results. Mitral regurgitation following acute aseptic inflammation seen as a finding in the present study correlate with the higher doses achieved by left atrium and left ventricle compared to other chambers of the heart .These findings correlate with the anatomy of the esophagus i.e Left atrium lies anterior to the esophagus [27].

Mitral valve regurgitation (MR) is a common target of postradiation damage, which can significantly affect long-term morbidity and mortality and may undermine the improved survival rate obtained with neoplasia treatment.3 The development of MR is a consequence of the restricted motion of thickened MV leaflets, which can occur alone or in the context of concomitant postradiation cardiac findings including aortic or tricuspid valve, pericardial, coronary, or myocardial involvement.[4, 5, 6, 7, 8] Surgical treatment, which may be required for some patients, is associated with high operative risk due to concomitant postradiation mediastinal and cardiac damage. [9, 10, 11, 12]. In particular, extreme radiation-induced calcification of the ascending aorta (“porcelain aorta”)is a harmful condition that can be prohibitive for open-chest surgery.

Bijl et al.[3] In their cross-sectional study of 82 HL survivors participated (52% men, mean age 47.8 years, 50 treated with MRT). Valvular disease was diagnosed by transthoracic echocardiography and compared between HL survivors treated with and without MRT. Univariate and multivariate logistic regression analysis was used to identify predictors for valvular disease. During a median follow-up of 13.4 years

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

(range 2 to 39 years), ≥ mild valvular disease was present in 61.2% of HL survivors with MRT (n = 30), compared with 31.0% of HL survivors without MRT (n = 9; odds ratio [OR] 3.51, 95% CI 1.32 to 9.30, p = 0.01). In multivariate analysis, only current age remained predictive for ≥ mild valvular disease (OR 1.08 per year, 95% CI 1.01 to 1.14, p = 0.023). Aortic regurgitation (AR) was most prevalent and irradiated patients had significantly more ≥ mild AR (38.2% vs 6.8%, p = 0.007). Within the MRT subgroup, time after radiation of >15 years was associated with AR (OR 4.70, 95% CI 1.05 to 21.03, p = 0.043), after adjusting for current age and hypertension.

Bouillon et al.[13] In their study on Long-Term Cardiovascular Mortality After Radiotherapy for Breast Cancer found that A total of 421 deaths due to cardiovascular diseases were observed, of which 236 were due to cardiac disease. Women who had received radiotherapy had a 1.76-fold (95% confidence interval [CI]: 1.34 to 2.31) higher risk of dying of cardiac disease and a 1.33-fold (95% CI: 0.99 to 1.80) higher risk of dying of vascular disease than those who had not received radiotherapy. It was a cardiovascular disease in 421 women, including cardiac diseases in 236 and other vascular diseases in 185 . The most frequent cardiac diseases were ischemic heart disease (n = 107), heart failure (n = 72), conduction disorders and cardiac dysrhythmias (n = 31), and the most frequent vascular causes were vasculocerebral disease (n = 108) and diseases of arteries, arterioles, and capillaries (n = 31).

Priya et al.[1] found that Mean Ejection fraction prior to Thoracic radiotherapy and after 6 months of radiotherapy was 57% and 52% (insignificant p value).

Saiki et al. [29] where they observed insignificant change in ejection fraction post thoracic irradiation.

Priya et al. [1] found that by 6 weeks of radiotherapy, 1 patient each in arm A(3DCRT) and B (IMRT) showed significant ECG changes(p-value= 0.406). By 6 months of radiotherapy, In ARM A, 5 patient ‘s and in arm B, 4 patient’s ECG showed bradycardia. In arm A, 2 patient’s ECG and in arm B, 3 patient’s ECG showed ST depression (p-value=0.544). ST changes can be a sign of Stage one pericarditis (inflammation of the pericardium). Also, bradycardia and Mitral valve regurgitation have a close correlation as concluded in the study by **Leichtman et al.** [30]. A study on cardiac toxicity where they observed biventricular diastolic

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

dysfunction post treatment irrespective of the modality [37].

Wethal et al. [14]found in a study on lymphoma patients post radiotherapy , of 116 patients observed approximately 10 years after treatment, 36 (31%) demonstrated moderate valvular regurgitation and in 40 patients, primarily either the aortic or mitral valve was involved, whereas none had evidence of stenosis. Interestingly, in the same cohort 39% of patients still available for follow-up 12 years later had developed aortic stenosis, including some of a moderate to severe degree (35%) . The valves were found to be thicker with reduced leaflet motion and calcification . These results suggest that valve retraction is the predominant early change that causes regurgitation and that it might take in excess of 20 years for the valves to become significantly thickened, calcified, and stenotic. It is hypothesized that a higher pressure system on the left side of the heart compared with the right accounts for why the mitral and aortic valves are affected more than the pulmonary and tricuspid. Multiple studies have supported the higher incidence of aortic and mitral valve disease [4,5,6,7]. Consistent with these observations, another study found that, of asymptomatic patients previously treated with at least 35 Gy of radiation, 6% had clinically significant dysfunction, and 26% had >grade II aortic regurgitation. Also, 26% demonstrated marked calcification of the aortomitral curtain .

Teimouri et al.[15] Studied changes in electrocardiography (ECG) and echocardiography(ECHO) following adjuvant RT were investigated in patients with left-sided breast cancer.The mean heart dose (±SD) for all patients was 7.51 ± 2.42 Gy. T-wave inversion was observed 3 months after RT in 47% of patients. T-wave decline was associated with mean heart radiation dose ($\beta = 0.605$, p-value = 0.005). This study showed that the left ventricular volume receiving the 5 Gy (LV-V5) parameter was associated with a reduction in ST segment duration (p-value = 0.027) as well as with an increase in left ventricular systolic diameter (LVESD, mm) (P-value = 0.027).

Haggeman et al. [16]In their study in Left sided Breast radiotherapy included 49 patients (38 patients received 3DCRT; 11 patients received IMRT; and 20 patients received neoadjuvant or adjuvant chemotherapy) magnetic resonance imaging (MRI) and echocardiography were performed before and at 6, 12, and 24 months after treatment.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

Mean heart dose for IMRT was 12.9 ± 3.9 Gy versus 4.5 ± 2.4 Gy for 3DCRT. Heart volumes receiving >40 Gy were 2.6% (3DCRT) versus 1.3% (IMRT); doses were >50 Gy only with 3DCRT. Temporary ejection fraction (EF) decrease was observed on MRI after 6 months (63%-59%, P=.005) resolving at 24 months. Only 3 patients had pronounced largely transient changes of EF and left ventricular enddiastolic diameter (LVEDD). Mitral (M) and tricuspid (T) annular plane systolic excursion (MAPSE and TAPSE) were reduced over the whole cohort (still within normal range). After 24 months left ventricular remodeling index decreased in patients receiving chemotherapy (0.80 vs 0.70, P=.028). Neither wall motion abnormalities nor late enhancements were found. On echocardiography, in addition to EF findings that were similar to those on MRI, global strain was unchanged over the whole cohort at 24 months after a transient decrease at 6 and 12 months. Longitudinal strain decreased in the whole cohort after 24 months in some segments, whereas it increased in others

Lindahl et al.[17] In their study on cardiovascular complication post breast radiotherapy found that after Two and six months after treatment ECG abnormalities were recorded in 30 and 47 per cent of the patients at rest and in 48 and 58 per cent during or after exercise. The numbers of different ECG items were almost the same as before treatment. The only exception was the increase in T-wave abnormalities two months and particularly six months after treatment (Table 2). Hypertension with left ventricular strain and digitalis glycosides may have contributed to the ST-T abnormalities in 5 and 8 patients, respectively. The more sensitive classification of T-wave abnormalities by the system of ATTERHOG & MALMBERG revealed the incidence of precordial T-wave changes already two months after treatment . T-wave changes appeared in 35 per cent of the patients. Six months after treatment the number of patients with T-wave changes was about the same as at two months after treatment but the changes were more marked. The flattening, deformity or inversion of the Twave usually was of the same magnitude in leads V2 and V4 and less severe in lead V5. usually exhibiting a reduced T amplitude only. Thus, the only significant ECG change after radiation therapy was an increase in T-wave abnormalities in leads reflecting the anterior wall of the heart. These ECG changes were correlated to the radiation dose absorbed by the heart, appearing in 8 per cent of patients receiving up

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

to 20 Gy and in 74 per cent of those given more than 20 Gy to the anterior quarter of the heart.

Tuohinen et al .[20] in their study on Radiotherapy-induced Early ECG Changes in Breast Cancer included Sixty eligible patients with chemotherapy-naïve left-sided and 20 with right-sided breast cancer were evaluated with echocardiography, blood samples and ECG before and after RT. Results: RT-induced ECG changes in the anterior leads. T-Wave changes were most frequent. T-Wave decline was associated independently with patient age ($\beta=-0.245$, $p=0.005$), mean heart radiation dose ($\beta=1.252$, $p=0.001$) and global systolic strain rate change ($\beta=7.943$, $p=0.002$). T-Wave inversion was associated independently with mean heart radiation dose ($\beta=0.143$, $p<0.001$), global longitudinal strain change ($\beta=0.053$, $p=0.017$) and posterior calibrated integrated backscatter ($\beta=-0.022$, $p=0.049$). They concluded RT-induced ECG changes were prevalent and associated with functional and structural changes in echocardiography.

They observed that RT induces electrocardiogram (ECG) changes in **13 to 37%** of patients with breast cancer . Changes in the ST segment and a reduction in R wave have been described in the early phase after RT , whereas changes in the T wave seem to be the most prevalent findings .Similar studies proved the same [31,32,33].

Son C et al. [21] studied Cardiac toxicity in patients with lung cancer receiving thoracic radiotherapy and immunotherapy. Of 194 ICI (immune checkpoint inhibitors)-treated patients evaluated, 55.2% (n=107/194) patients had received thoracic RT at a median dose of 60.4 Gy (range, 15-75). Cardiotoxicities such as non-ST elevated myocardial infarction and new onset supraventricular tachycardias were observed in 13 (12.2%) of those who had thoracic RT versus 9 (10.3%) who did not ($p=0.87$). 38 patients who received RT concurrently with ICI did not develop any cardiotoxicity whereas 14.1% (n=22/156) of those who did not receive concurrent RT developed cardiotoxicities (univariate, $p=0.030$; multivariate, $p=0.055$). There were no significant differences in the mean heart RT dose, Framingham risk score, and steroid treatment between patients that received concurrent RT with ICI versus non-concurrent RT/ICI.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

Mulrooney et al. [35] in their study on Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer found that Exposure to 250 mg/m(2) or more of anthracyclines increased the relative hazard of congestive heart failure, pericardial disease, and valvular abnormalities by two to five times compared with survivors who had not been exposed to anthracyclines. Cardiac radiation exposure of 1500 centigray or more increased the relative hazard of congestive heart failure, myocardial infarction, pericardial disease, and valvular abnormalities by twofold to sixfold compared to non-irradiated survivors. The cumulative incidence of adverse cardiac outcomes in cancer survivors continued to increase up to 30 years after diagnosis.

Porela et al. [33] study made observations which show that PR segment analysis is a powerful tool in the differential diagnosis of myopericarditis and STEMI. This simple information should be added to the diagnostic workup of patients presenting with ST elevations. In myopericarditis, the most common location for PR depression was lead II (55.9%), while this ECG finding least likely appeared in lead aVL (2.9%). PR depression in any lead had a high sensitivity (88.2%), but fairly low specificity (78.3%) for myopericarditis. The combination of PR depressions in both precordial and limb leads had the most favorable predictive power to differentiate myopericarditis from STEMI (positive 96.7% and negative power 90%).Pruitt et al. [34] found A correlation of the clinical and electrocardiographic findings was undertaken in 110 cases which had in common the presence of deeply inverted T waves in central terminal leads centered about position 3 on the precordium.Patients treated before age 45 experienced a higher CVD (95% CI, 1.3-3.1).

They concluded that Currently, a large population of breast cancer survivors is at increased risk of death from CVDs and second cancers, especially when treated with RT at a young age. Patients irradiated after 1979 experience low (postmastectomy RT) or no (postlumpectomy RT) excess mortality from CVD.

Mediastinal radiotherapy is a known risk factor for the development of cardiovascular diseases affecting the coronary arteries, pericardium, myocardium, conduction system, and myocardial valves .Higher pressure on the left side of the heart likely explains the observation that the aortic and mitral valves were affected more often than the

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

tricuspid or pulmonary valves, and that stenosis is primarily observed in the aortic valve[38,39,40].

CONCLUSION - Cardiovascular disease is an important cause of mortality post thoracic irradiation .Various studies have concluded that most commonly ST segment and T wave inversion are found in ECG in correlation with functional and structural changes in ECHO where Valvular regurgitation and Cardiomyopathy are commonly observed. Highly conformal radiotherapy and careful planning can prevent future cardiovascular complications and can decrease mortality due to the same.

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TABLE 2 - ***STUDIES ON CARDIOVASCULAR COMPLICATIONS POST RADIOTHERAPY AND THEIR MAJOR FINDINGS***

STUDY	**SITE OF CANCER TREATED**	**RADIOTHERAPY MODALITY USED**	**MAJOR ECG FINDING/MRI FINDING**	**MAJOR ECHO FINDING**
Priya et al.	ESOPHAGUS	3DCRT (ARM A) IMRT(ARM B)	BRADYCARDIA, ST DEPRESSION IN V4-6	LEFT VENTRICULAR DYSFUNCTION , MITRAL REGURGITATION
Bijl et al.	HODGKIN'S LYMPHOMA	IMRT	-	AORTIC REGURGITATION
Bouillon et al.	BREAST	COBALT	DYSRRHYTHMIA	VENTRICULAR DYSFUNCTION
Wethal et al.	Hodgkin's lymphoma	2DRT	-	MITRAL AND AORTIC REGYGITATION , VENTRICULAR DYSFUNTION
Teimouri et al.	Left Breast	3DCRT	ST DEPRESSION , T WAVE	LV DIASTOLIC DYSFUNCTION

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

			ABNORMALITIES	
Heggeman et al.	Left Breast	3DCRT IMRT	TRANSIENT DECREASE IN LVEF	TRANSIENT DECREASE IN LVEF,LV DYSFUNCTION
Lindahl et al.	Breast	COBALT	ST SEGMENT AND T WAVE ABNORMALITIES	-
Tuohinen et al.	Breast	3DCRT	ST SEGMENT AND T WAVE,PQ ABNORMALITIES	CARDIOMYOPATHY (STRUCTURAL AND FUNCTIONAL CHANGES)
Son C et al.	Lung	Conformal	NSTEMI,SVT	VENTRICULAR DYSFUNCTION