International Journal Dental and Medical Sciences Research (IJDMSR)
ISSN: 2393-073X Volume 4, Issue 10 (October - 2020), PP 05-12
www.ijdmsr.com

Cardiac Profile of Patients Treated For Various Malignancies At A Tertiary Cancer Centre.

Syed Arshad Mustafa[1*], Mushood G Nabi[1*],
Syed Manzoor Ali Andrabi[2*], Mohd Ismail[3*]
[1]Associate Professor Radiation Oncology, [2]Associate Professor Internal Medicine,
*[3]Professor Internal Medicine * Government Medical College Srinagar, J&K, India*
**Corresponding Author: Syed Manzoor Ali Andrabi[2]*

ABSTRACT: -
Background: Improvements in *cancer care* worldwide has resulted in sufficient survival length for cancer patients to experience treatment related toxicities. Cardio toxicity is a well known sequel of cancer treatment. Detection of cardiac dysfunction using various parameters in patients treated for malignancies is important as it may facilitate early therapeutic / preventive measures.
Aims & objective: To analyse the echocardiographic profile of patients treated with chemo-immuno-radiotherapy for various malignancies
Materials & Method: Cardiac profile of seven hundred fifty two (752) cancer patients was analysed in year 2019 with 2D Echocardiography.
Results:
Conclusion : Chemo-Radiotherapy-Immunotherapy induced cardiac effects are often subtle & under reported. Proper assessment prior & after therapy is warranted to avert or minimise the side effects**.** There is a scope for collaboration between oncologists and cardiologists to improve the care of oncology patients receiving cardio toxic therapy.

Keywords: cancer, chemo-radio-targeted therapy, 2D Echo, cardio- toxicity ,

I. INTRODUCTION:

Cardiac dysfunction resulting from cancer treatment was recognized almost six decades back, when anthracyclines were widely used for the treatment of various malignancies. **(1)** Heart failure (HF) associated with anthracyclines was then recognized as an important side effect.

With improvised cancer care worldwide , survival in cancer patients has improved a lot leading to treatment related morbidities which were hitherto unaccounted for & not appreciated that much. **(2)** These side effects have become an issue for cancer survivors. Of the various toxicities expected from cancer treatment, cardiac events are the most feared ones, so much so that the gain in life expectancy due to improvised cancer care is countered by increased morbidity & mortality due to adverse cardiac events**.** **(3)**

Cancer management has evolved as a multimodality discipline involving radiotherapy(loco regional treatment) & systemic anticancer therapy-(SACT) which includes chemotherapy & targeted -therapy , each with its own bearing on cardiac profile.

Cardio-oncology as a subspeciality is rapidly growing field worldwide. It has helped minimize the effects of cardiovascular morbidity and mortality in cancer survivors by stratifying patients at baseline, & defining the risk of cardiotoxicity with respect to various anti cancer treatment modalities to be under taken. **(4)**

Cancer treatment can put patients at risk for a variety of cardiovascular complications including heart failure, coronary artery disease, peripheral vascular disease, thromboembolism, pericardial disease and valvular heart disease. Those patients receiving therapy with known cardiac risk require close monitoring during and after treatment.

Echocardiography plays an essential role in the early detection of many of these complications**.** **(5)** Cardiotoxicity in the form of left ventricular dysfunction is the primary focus of this study & the role of echocardiography thereof.

As far as chemotherapy induced morbidity is concerned , various factors implicated include type of drug used , cumulative dose, dose administered at each cycle, route & schedule of administration, combination of other cardiotoxic drugs and/or association with radiotherapy apart from patient related factors like age,

presence of cardiovascular (CV) risk factors, history of previous cardiovascular disease (CVD) & prior mediastinal radiation therapy. [6]

Targeted therapies are a novel addition to SACT algorithim. However their scope has been steadily increasing in more & more cancers over the years, owing to their promising results in prolonging the disease free survival (DFS) & overall survival(OS) albeit with accompanying toxicity(s). [7]Cardiovascular side effects are most worrisome with the use of targeted therapies. [8]

Various determinants affecting cardiac outcome in radiotherapy include mode of radiation beam delivery (EBRT or brachytherapy), total dose delivered, dose per fraction & overall treatment duration. [9]

RT-induced heart disease has often offset the improvements in cancer-specific survival provided by adjuvant RT in some curable malignancies requiring thoracic RT . [10]

But over the years mode & precision of radiation delivery has improved a lot. This has led to a significant reduction in radiation induced cardiac morbidity & subsequent mortality**.** [11]

The key principle of minimising normal tissue irradiation whilst providing the optimum dose to the cancer target dictates that factors such as tumour location, histology, stage & grade plus patients performance be taken into consideration before contemplating radiation treatment.

II. MATERIAL & METHODS

This was a retrospective non randomised analysis conducted in year 2019 on 752 evaluable cancer patients who received treatment in the department of radiation oncology SMHS Hospital, Srinagar. We studied the outcome of chemo-radio-targeted therapy on cardiac profile of those cancer patients who otherwise had no significant cardiac history. Patients with pre existent cardiac morbidities like myocadial infarction, acute coronary syndrome, cor pulmonale, patients on pacemaker, baseline ejection fraction (EF) less than 50% were excluded . Patients with low performance score (ECOG 3 or 4) were also excluded from the analysis. However patients who were diabetic & hypertensive and had controlled parameters on medicines were included in this study. Patients who received only non-thoracic /non-meditational radiation therapy as the sole modality of treatment were not included in this study(CNS, head & neck cancer receiving only radiation therapy & Skin cancers) nor were haematological malignancies . In head & neck cancers, only those patients were included who had received either chemo&/or Targeted therapy along with other modality(s).

All enrolled patients had a baseline cardiac evaluation done by a cardiologist in the form of electro cardiogram, echocardiogram or any other investigation deemed necessary by the cardiologist. All echos were 2D trans thoracic & were done before , at completion & at 6 months post treatment. Treatment was interrupted or stopped in patients whose ejection fraction dropped to less than 55% or if there was a 10% decline in EF from baseline. Moreover, patients who had defaulted in between were also not considered eligible.

Radiotherapy was delivered by a External Beam Telecobalt Unit (*Siemens*), chemotherapy included various cytotoxic drugs in infusion as well as bolus form. Targeted therapy was given in the form of either oral drugs(Tyrosine Kinase Inhibitors , Selective Estrogen Receptor Modifiers) or intravenous infusions(anti VEGFs, EGFRs & Immunomodulators).

III. RESULTS:

From January 2016 to December 2018, seven hundred & fifty two eligible (752) patients were enrolled in this study which was carried out in the departments of *Radiation Oncology & Internal Medicine* , GMC Srinagar**(Table 1).** Out of 752 patients 428(57%) were males & 324(43%) were females. Eighteen percent(18%) were<40years, over forty percent (42%)patients were in the age group 41 -60 years & thirty eight percent (38%)> 60 years of age. Sixty percent(60%) were from rural areas & seventy eight(78%) percent of the patients used tobacco in one or the other form. Majority of the patients had BMI in the range of 18-25 which was equally distributed in both the genders. Only one third(33%) of the patients had a history of regular exercise, which was predominant in males . Eldest patient was a male of eighty four years while fourteen year old girl was the the youngest patient. **(Table 1)**

Table: 01 Patient characteristic

	DEMOGRAPHICS			
S No			Male (%)	Female(%)
	Total =752		428(57%)	324(43%)
1.	Age	<40=	95 (12.6%)	42 (5.5%)
		40-60=	205 (27.2%)	122 (16.2%)
		>60=	128 (17%)	160 (21.2%)
2.	Residence	Rural	261(35%)	213(28%)
		Urban	167(22%)	111(15%)

3.	Tobacco use	586(78%)	521(69%)	65(9%)
4.	Alcohol	11(1.4)	11(1.4)	0
5.	Exercise	248(33%)	208(27%)	40(6%)
6.	BMI	<18.5	123(16%)	58(8%)
		18-25	226(30%)	195(26%)
		>25-30	79(11%)	71(9%)

Table: 02 System wise Incidences

NO.	SYSTEM	NUMBER	PERCENT(%)
1	Lung	114	15.16
2	Colorectal	103	13.70
3	Gastric	99	13.16
4	Breast	90	11.96
5	Esophagus	77	10.23
6	Lymphoma	59	7.84
7	Genitourinary	48	6.38
8	Ovary	42	5.58
9	Hepatobiliary	29	3.85
10	Head &Neck	22	2.92
11	Occult Primary	21	2.79
12	Sarcoma	18	2.39
13	Myeloma	11	1.46
14	Neuroendocrine	6	0.79
15	Uterine	4	0.53
16	Mesothelioma	4	0.53
17	Cervix	3	0.39
18	Thymoma	2	0.26
	Total	752	100

Gastrointestinal cancers outnumbered all malignancies & were nearing 40% of all cancers. Followed by lung (15%)& breast (11.9%). Thymoma was the least common malignant tumor registered (0.2%). **(Table 02)**

Table: 03 Treatment modalities used for various malignancies

S no	System	Chemo only	Radiation only	Targeted only	Chemo radiation	Chemo-targeted	Radiation targeted	Chemo-radiation-targeted
1.	Lung	25	09	12	52	07	06	03
2.	Colo-rectal	70	-	-	-	33	-	-
3.	Gastric	25	05	-	45	15		09
4.	Breast	10	02	05	17	11	03	42
5.	Esophagus	08	12	-	44	07	-	06
6.	Lymphoma	17	07	-	03	27	-	05
7.	Genitourinary	16	-	09	21	02	-	-
8.	Ovary	36	-	-	-	06	-	-
9.	Hepatobiliary	17	-	-	05	07	-	-
10.	Head & Neck	07	-	-	10	05	-	-
11.	Occult primary	12	-	-	05	04	-	-
12.	Sarcoma	08	03	-	07	-	-	-
13.	Myeloma	02	01	05	-	03	-	-
14.	Neuroendocrine	03	-	-	03	-	-	-
15	Uterine	04	-	-	-	-	-	-
16.	Mesothelioma	03	-	-	01	-	-	-
17.	Cervix	02	-	-	01	-	-	-
18.	Thymoma	-	02	-	-	-	-	-

Most of the malignancies nearly required all the modalities of treatment, whileas there were few cancers like lymphoma, lung, esophageal & gastric which warranted radiation as the sole modality of treatment. They required thoracic or meditational radiotherapy & had a bearing on the cardiac outcome due to the treatment. **(Table 3)** Over thirty five percent of patients (265) received chemotherapy only while as a little over 5% (41) patients received only RT.

The percentage of patients receiving combined chemo-RT, chemo-targeted, chemo-RT-targeted, RT-targeted & only targeted therapy were 28.4 %(214), 16.8%(127), 8.6%(65), 1.1%(09)& 4.1%(31) respectively. **(Table3)**

Chemotherapy was the commonest modality used followed by combined chemo-RT, whereas patients receiving 'targeted therapy – RT' were lowest in number. **(Table 03)**

Table: 04 commonly used Chemotherapy/Targeted regimens

Types of chemo-therapy/primary	Platinum	Gem	Vp-16	Pem	Tax	FU/Cap	Dox	CTX/Ifos	Vinca	Targeted	Hormones
Lung	+	+	+	+	+				+	+	
Colorectal	+					+				+	
Gastric	+				+	+				+	
Breast	+	+			+	+	+	+		+	+
Esophagus	+				+	+				+	
Lymphoma							+	+	+	+	
Genitourinary	+	+			+						
Ovary	+	+			+	+		+		+	+
Hepatobiliary	+	+				+				+	
Head &Neck	+				+	+				+	
Occult Primary	+				+					+	
Sarcoma	+						+	+	+	+	
Myeloma										+	
Neuroendocrine	+		+								
Uterine	+										
Mesothelioma	+			+					+		
Cervix	+				+						
Thymoma	+		+				+	+	+		

Platinum, taxanes & FU were the commonest cytotoxic drugs used, & targeted therapy was used in twelve out of the fourteen evaluated cancers. **(Table 4)**

Table: 05 'Mean heart dose' of radiation received in various malignancies

S no	Primary	Total radiation dose in Gy	Dose /fraction	Mean heart dose Gy	Mode/beam configuration/source
1	Esophageal	50-60	1.8-2	24	EBRT/ Photon/ Co^{60}
2	Mediastinal lymphoma	30-45	1.8-2	18	"
3	Lung	45-65	1.8-2.2	22	"
4	Breast	45	1.8-2	05	"
5	Thymoma	45-55	1.8-2.2	11	"
6	Gastric /GE junction	40-45	1.8-2	09	"

Radiation dose to heart was calculated for each malignancy requiring thoracic, chestwall or mediastinal RT using *XiO, Elekta* treatment planning system. Esophageal cancers had the maximum mean cardiac dose whereas breast had the least**.(Table 5)**

Table : 06 Echocardiographic profile(EF) after treatment

S No	Modality	Average Pre-treatment echo(EF) %	Average Post treatment echo(EF)%	Average Follow up echo(EF) %
1	Chemo only	68	64	65
2	Radiation only	67	62	63
3	Chemo radiation	72	69	66
4	Chemo-targeted	67	62	61
5	Radiation targeted	66	63	60
6	Chemo-radiation-targeted	67	62	60

Mean echo in the pre-treatment, post-treatment & follow-up setting of various malignancies was 67%, 63.6% & 62.5% respectively. Highest depreciation in the EF was seen in patients who received 'chemo-RT-targeted' therapy & 'chemo-radiation'(07% &06%respectively). **(Table 06).**

IV. DISCUSSION:

Cardio-oncology as a separate subspeciality is rapidly growing field, with the primary aim of minimizing the effects of cardiovascular morbidity and mortality in cancer survivors. To meet this, patients are assessed at baseline to define their risk of cardiotoxicity and then followed closely during and after treatment to assess for early signs or symptoms of cardiovascular disease. With the advent of improvised cardiological gadgets, there has been ample choice for diagnoses of even subtle cardiac dysfunction. [(11)]
The incorporation of modern techniques such as myocardial contrast echocardiography, three-dimensional (3D) echocardiography (3DE), Doppler tissue imaging (DTI), and
speckle-tracking echocardiography (STE), offer a prudent compromise between cost-effectiveness and clinical predictive value. Multiple gated acquisition(MUGA) myocardial scintigraphy allows a very reliable assessment of LVEF, but its use is limited because of radiation exposure. [(12)]

Magnetic resonance imaging (MRI), used to assess myocardial function, to evaluate myocardial perfusion and for tissue characterization, is not an ideal first-line screening test at present, but may have potential in the future. With cardiac computed tomography (CT) image quality is better than MRI but, because of considerable radiation dose, it is not considered a useful method to assess cardiac function [(03)]

Coronary computed tomography angiography (CCTA) is an appealing option but detection remains limited to those without significant coronary calcifications. [(13)] Radiation exposure has been a concern but recently developed CT scanners have led to dose reduction. The role of cardiac MRI remains to be defined but it is an excellent method to reliably assess ventricular structure and function and can be used for perfusion stress imaging. However, it poses significant logistic and financial challenges.[(14)]

However of the various modaliteis, two of them have evolved over time to be very useful: endomyocardial biopsies and monitoring of left ventricular ejection fraction (LVEF) by cardiac imaging. Earliar end myocardial biopsies proved to be the most sensitive and specific parameter for the identification of anthracycline-induced LV dysfunction and became the gold standard in the 1970s.[(15)] However, the interest in endomyocardial biopsy has diminished over time because of the reduction in the cumulative dosages used to treat malignancies, the invasive nature of the procedure, and the remarkable progress made in non-invasive cardiac imaging.

The non-invasive evaluation of LVEF via 2D Echocardiography has gained importance, and notwithstanding the limitations of the techniques used for its calculation, has emerged as the most widely used strategy for monitoring the changes in cardiac function, both during and after the administration of potentially cardio toxic cancer treatment [(12)]

Echocardiography has become the cornerstone in the 'cardiac imaging evaluation' of patients in preparation for, during, and after cancer therapy, because of its wide availability, easy repeatability, versatility, lack of radiation exposure, and safety in patients with concomitant renal disease. In addition to the evaluation of LV and right ventricular (RV) dimensions, systolic and diastolic function at rest and during stress, echocardiography also allows a comprehensive evaluation of cardiac valves, the aorta, and the pericardium. [(16)]
Cardiac imaging, and in particular, transthoracic echocardiography, plays an essential role in the baseline assessment and serial follow-up of cardio-oncology patients. [(12)]

The objective of this paper was to highlight the cardiac sequelae of cancer treatment & review the mechanisms of cardio toxicity of various modalities used & to outline a framework for future course of action in these patients.

Chemotherapy-induced cardio toxicity has been variously defined, either as symptoms or signs of heart failure (HF), five percent reduction in LVEF from baseline to <55% LVEF in the presence of signs or symptoms of HF, or a reduction in LVEF of ≥10% to <55% without signs or symptoms of HF. [(17)] Most recently, cancer therapeutics-related cardiac dysfunction (CTRCD) was defined as a drop in LV EF of ≥5% in symptomatic patients or a drop in LV EF of ≥10% to an EF of <53% in asymptomatic patients.[(18)]Two types of CTRCD have been described. Type 1 is an irreversible, dose-dependent toxicity that results from ultra-structural changes in the myocardium. This type of cardiac injury is typified by Anthracyclines. There are several hypotheses regarding the mechanism of cardiotoxicity from anthracyclines, but the generation of free radicals and subsequent cellular damage is accepted as a central cause.

Other mechanisms proposed are either due to a direct effect on cardiovascular system , alteration in the coagulation profile , hemodynamic status, arrhythmogenic effects and pericardial inflammation associated with myocardial dysfunction or pericardial sequels.(**Table 7**) [(19)]
Cardiotoxicity profile of each chemotherapeutic drug(s) varies & is affected by concomitant use of other modalities like radiation, targeted & immuno- therapies. [(20)]

In our study majority of the patients received platinum, FU & taxane based chemotherapies **(Table 08)**. Decrease in EF (ejection fraction) was not seen in any of the patients receiving these chemotherapies as the only mode of treatment. Twelve patients who received anthracyclines & herceptin had a 5% fall in EF post treatment. One patient on maintainence herceptin has acute fall in EF for which her treatment had to be interrupted. On subsequent analysis her echo was within normal rnage and she resumed her treatment after dose reduction & close cardiac monitoring.

Table : 7 Cardio toxicity profile of various drugs

S no	Drug family	Common Cardiotoxiciy
1	Anthracyclines	Heart failure (irreversible)
2	Taxanes	Heart block, brady cardia , tacharrythmia
3	Platinums	Acute coronary syndromes
4	Antimetabolites	Coronary vasospasms
5	Anti EGFR*	Heart failure(reversible)
6	Anti VEGF**	Hypertension, thromboembolism
7	TKIs***	Hypertension, heart failure, MI

* Anti epidermal growth factor receptor
** Anti vascular endothelial growth factor
*** Tyrosine kinase inhibitor

Over the last half century, radiation therapy has evolved to become one of the cornerstones of treatment of various types of cancers. It is estimated that >50% of patients with cancer are treated with radiotherapy (RT). Along with the development of novel chemotherapeutic agents, radiation therapy has revolutionized the prognosis of patients with various cancers. [(21)]

Historically,patients with mediastinal malignancies or lymphoma who received mediastinal or "Mantle" radiation were seen to be at high risk for cardiovascular complications, particularly if received during childhood. [(22)] However with the advent of modern radiation delivery equipments which deliver radiation to the precise target area of interest, radiation complications have been reduced to a great extent . [(11)]

Emerging evidence suggests that older women with breast cancerwho receive radiation therapy are also at an increased long-term risk of cardiovascular morbidity and mortality. [(23)]
Radiation therapy induces a spectrum of cardiotoxicities that differ considerably from chemotherapy-related cardiotoxic effects and affect all layers of the heart.

The pathological outcome of therapeutic irradiation can be broadly reduced to four conditions: pericarditis, pericardial fibrosis, diffuse myocardial
fibrosis, and coronary artery disease (CAD). [(24)]Radiation may also cause valvular disease, although the evidence for this is not as strong[(25)]

In the acute setting, the most common complication is asymptomatic pericardial effusion. Acute pericarditis though less common presents with similar symptoms as nonspecific pericarditis. In the chronic setting, constrictive pericarditis can develop which is difficult to distinguish clinically from restrictive cardiomyopathy as both present with diastolic dysfunction.

In our analysis, esophageal, lung, breast & lymphoma(mediastinal) were the prime malignancies for which RT was delivered**(Table 08)** of which only **s**ix patients of lung cancer on combined chemo-RT had 05% drop in EF and were symptomatic. One patient amongst them developed pericarditis & pericardial effusion which was drained twice.

Chronic valvular complications are also seen after radiation therapy, most commonly aortic and mitral stenosis. [(22)] Coronary artery disease in the absence of traditional risk factors is another potential chronic complication of radiation therapy, however is better evaluated by other imaging modalities including coronary invasive or CT angiography.

Radiation therapy treatment involves utilization of high-energy particles, X-rays, or gamma rays that fragment cellular DNA and thereby interfere with cell proliferation and viability. Nowadays use of sophisticated gadgets ,modifications of radiation protocols, careful radiation field planning, and techniques have helped to reduce the radiation dose to the normal cardiovascular structures. [(26)]

Molecular targeting agents ,Hormonal therapies, and immunotherapy's are more specific in their mode of action. Their cardio toxicity risk can occur via a number of mechanisms. One is direct 'on-target toxicity' by inhibition of human epidermal growth factor resulting in myocyte injury and impaired systolic function (e.g. trastuzumab.) Second is indirect, 'on-target toxicity' (e.g. GnRH agonists for prostate cancer which increase LDL and diabetes risk leading to atherosclerosis and increased risk of myocardial infarction). Third is 'Off target toxicity' where the drug appears to inhibit a range of molecular targets, not only the principle target molecule in the cancer, but inhibition or activation additional pathways that impart cardiovascular risk (e.g. sunitinib-which displays both on-target and off-target toxicity.) [(27)]

Like Trastuzumab other TKIs which cause typeII injury are lapatinib, pertuzumab, imatinib, sorafenib, sunitinib, bevacizumab and bortezomib. **(Table 7)** [(28)]

Our analysis did not depict any significant acute or early reduction in EF. What could be inferred is that there was careful selection of patients for the treatment, carefully planned radiation portals & vigorous follow up with cardiologist so as to modify radiation treatment plan or drug dosage as per the clinical situation.

Table: 8

S : NO	Cancer treatment modality	Examples
1	Cytotoxic chemotherapy	Anthracyclines, taxanes, platinums, antifolates
2	Radiation therapy	Breast, lung, esophagus, lymphoma (mediastinal)
3	Targeted therapies	Trastuzumab, sunitinib, bevacizumab, imatinib
4	Hormonal therapies	Tamoxifen, letrozole, abiraterone

V. CONCLUSION:

There should be an emphasis to identify subclinical and other cardiac dysfunctions early, in order to allow cancer patients and their physicians to make informed decisions about therapeutic options. Echocardiography is a readily available non-invasive tool to measure cardiac function and plays a major role in the diagnosis of cardio toxicity. The purpose of this study was to focus on the pre emptive measures to be undertaken before starting cancer treatment & role of cardiologist in averting or minimising untoward complication(s) arising post treatment with relevance to echocardiography in detecting cardio toxicity.

Hence the likelihood of avoiding or reducing the cardio toxic effects of these agents while improving the oncologic benefits of the therapy can be increased by close collaboration between the oncologist and cardiologist.

BIBLIOGRAPHY

[1]. Smith LA, Cornelius VR, Plummer CJ et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-analysis of randomised controlled trials. B MC Cancer 2010; 10:337.

[2]. Shakira DK, Rasul KI. Chemotherapy Induced Cardiomyopathy: Pathogenesis, Monitoring and Management. J Clin Med Res. 2009;1(1):8-12.

[3]. Bovelli D, Plataniotis G , Roila F. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. Annals of Oncology. 2010; 21: 277-82.

[4]. Tan TC , Crosbie MS . Assessing the Cardiac Toxicity of Chemotherapeutic Agents:Role of Echocardiography. Curr Cardiovasc Imaging Rep. 2012 (December) 1; 5(6): 403–409.

[5]. Larsen CM , Mulvagh SL .Cardio-oncology: what you need to know now for clinical practice and echocardiography. Echo Res Pract. 2017 Mar; 4(1): 33–41.

[6]. Hamirani Y, Fanous I, Kramer CM et al. Anthracycline- and trastuzumab-induced cardiotoxicity: a retrospective study. Med Oncol. 2016 July ; 33(7): 82.

[7]. Le DL, Cao H , Yang LX. Cardiotoxicity of Molecular-targeted Drug Therapy. Anticancer Research. 2014 July;34(7):3243-3249.

[8]. Chen Z, Ai D. Cardiotoxicity associated with targeted cancer therapies. Molecular and clinical oncology.2016 May;4(5): 675-681

[9]. Yusuf SW, Venkatesulu BP , Mahadevan LS. Radiation-induced Cardiovascular Disease: A Clinical Perspective. Front Cardio-vasc Medicine.2017;4:66.
[10]. Aleman BM, Belt-Dusebout AW, Klokman WJ, et al. Longterm cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 2003;21:3431–3439.
[11]. Korreman SS, Pedersen AN, Aarup LR et al. Reduction of cardiac and pulmonary complication probabilities after breathing adapted radiotherapy for breast cancer. Int. J. Radiation Oncology Biol. Phys.2006 ; 65(5): 1375–1380.
[12]. Plana JC, Galderisi M, Barac A .Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging European Heart Journal – Cardiovascular Imaging .2014; 15: 1063–1093.
[13]. Kruk M, Noll D, Achenbach S, et al. Impact of Coronary Artery Calcium Characteristics on Accuracy of CT Angiography. JACC. Cardiovascular imaging. 2014 Jan;7(1):49-58.
[14]. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. Journal of Clinical Oncology. 2004; 22:3139–3148.
[15]. Torti FM, Bristow MM, Lum BL. Cardiotoxicity of Epirubicin and Doxorubicin: Assessment by Endomyocardial Biopsy. Cancer Research.1986; 46: 3722-3727.
[16]. Mahabadi AA, Rischpler C. Cardiovascular imaging in Cardio-Oncology. Journal of thoracic diseases. 2018;10(Suppl 35):4351-4366.
[17]. Seidman A, Hudis C, Pierri MC, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol .2002;20:1215-1221.
[18]. Plana JC, Galderisi M, Barac A, *et al*. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal: Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2014 Oct;15(10):1063-1093.
[19]. Gillespie HS, McGann CJ, Wilson BD – Noninvasive diagnosis of chemotherapy related cardiotoxicity. Curr. Cardiol. Rev. 2011;7:234-244.
[20]. Florescu M, Cinteza M, Vinereanu D. Chemotherapy induced cardiotoxicity. Maedica. Journal of clinical medicine. 2013;8(1): 59-67.
[21]. Bleyer WA. The impact of childhood cancer on the United States and the world. CA Cancer J Clin 1990;40:355-367.
[22]. Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. J Clin Oncol. 1993;11(7):1208–1215.
[23]. McGale P, Darby SC, Hall P, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. Radiother Oncol. 2011;100(2):167–75.
[24]. Fajardo, LF, Berthrong, M, Anderson RE. Radiation pathology. J Clin Pathol. 2002; 55(6): 480.
[25]. 25.Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: Is the epidemiologic evidence compatible with the radiobiologic data? Int J Radiat Oncol Biol Phys. 2007; 67:10–18.
[26]. Herrmann J, Lerman A. Evaluation and Management of Patients With Heart Disease and Cancer: Cardio-Oncology Mayo Clin Proc. 2014 ; 89(9): 1287–1306.
[27]. Svoboda M , Poprach A, Dobes S, et al. Cardiac Toxicity of Targeted Therapies used in the Treatment for Solid Tumours: A Review. Cardiovasc Toxicol. 2012 ;12:191–207.
[28]. Meyersohn NM, Pursnani A, Neilan TG. Detection of Cardiac Toxicity Due to Cancer Treatment: Role of Cardiac MRI. Curr Treat Options Cardio Med.2015; 17: 38.

Corresponding Author: Syed Manzoor Ali Andrabi
Associate Professor Internal Medicine, * Government Medical College Srinagar, J&K, India
PIN: I90010 Cell NO: 9419006441