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Evaluating the effects of esophageal and breast cancer radiotherapy on the cardiac function and determining the relationship between the dosimetric parameters and ejection fraction changes

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ABSTRACT

Background: In the radiotherapy of patients with esophagus and breast cancer, the heart receives a significant dose of radiation that might cause heart complications. Thefore, the aim of the current study was to evaluate the effects of esophagus and left breast cancer radiotherapy on the cardiac function and to determine the relationship between the dosimetric parameters and ejection fraction (EF) changes. ***Materials and Methods***: Patients with esophageal (n=13) and left breast cancer (n=21) enrolled at our radiotherapy center from March to October 2017. Echocardiography tests were obtained from patients, before and six months after the radiotherapy. Dosimetric parameters were extracted from treatment planning system. The assessed outcomes included pre- and post-radiation EF ratios and percentage change in the EF following radiation. ***Results:*** The mean ± standard deviations of EFs in patients with breast cancer before and six months after treatment were 55.95%±3.2% and 53.10%±6.30% respectively, which were not statistically significant (P = 0.07). In patients with esophagus cancer, the mean ± standard deviations of pretreatment and post-treatment EFs were 56.76%±3.44% and 52.09%±3.88% respectively, which were statistically significant (P = 0.005). ***Conclusion:*** The results of our study showed a significant variation of EFs in esophageal cancer patients following radiotherapy, while breast cancer patients treated with radiotherapy showed no significant change. In patients with esophagus cancer, there was a significant correlation between the variation of EFs and volume of heart receiving radiation doses ≥30 Gy (≥V30). Therefore, to avoid reduction in EF, the use of V20 as a dose-volume constraint is recommended.

Keywords: *Radiation therapy, cardiac function, breast cancer, esophagus cancer, echocardiography.*

INTRODUCTION

Breast cancer is the second-most-common cancer and the main cause of death from cancer among women in the world. Breast cancer includes 33% of women's cancer and 19% of cancer-related deaths among women [(1)]. Esophageal cancer is the eighth-most-common cancer and the sixth cause of cancer deaths in the world [(2)]. Esophageal cancer is the second-most-common cancer among men and the third-most-common cancer among Iranian women [(3)].

In the radiotherapy of patients with

esophageal and left breast cancer, though the tumor is directly irradiated, the heart is also exposed some unwanted radiation [4]. In the radiotherapy of patients with right breast cancer, the heart does not receive any significant dose of radiation that might cause heart complications [5, 6].

The amount of radiation received by the heart due to radiotherapy is associated with short-term and long-term cardiac complications. Long-term side effects of the heart due to irradiation include myocardial fibrosis, conduction defects, accelerated coronary artery disease, valvular problems, and delayed pericarditis. The most common acute heart complication due to irradiation is pericarditis, which is, of course, usually limited [4, 7]. Studies have also shown that a radiation dose received by the heart causes changes in the left ventricle ejection fraction (LVEF) and leads to heart complications [8, 9].

According to the American Society of Echocardiography and the European Association of Cardiovascular Imaging report, the normal LVEF for adults over 20 years of age is 53-73% [10]. Mukherjee *et al.* [9] have shown that, in esophageal cancer patients, chemoradiotherapy (CRT) significantly reduces the cardiac ejection fraction from the baseline (EF=63%). Previous studies have revealed that cardiac complications due to radiotherapy are related to the dose of radiation received by the heart [7, 11]. Therefore, a volume of the heart that receives a given dose is important and can be evaluated. In several studies, the relationship between dosimetry parameters and cardiac complications of radiotherapy has been investigated [7, 11-14].

Several methods have been employed to diagnose cardiac complications such as biomarkers and CT images [4, 13]. But studies have shown that an increase in the number of biomarkers is not related to the variation of the ejection fraction [15, 16]. In addition, the radiation dose received by the patient due to CT scan is relatively high and there is a probability of complications, such as increased cancer induction risk [17]. This has been confirmed by the report of the International Commission on the Radiological Protection Special Task Force [18].

Owing to its easy accessibility, reliability, and lack of ionization radiation, echocardiography can be used as the basis for cardiac imaging to evaluate patients for cardiac complications before and after cancer therapy with radiation. Echocardiography also allows for a complete assessment of left and right ventricular dimensions, and systolic and diastolic activities in relaxed and stressed conditions, as well as for a complete evaluation of the heart, aorta, and pericardium [19].

Using quantitative echo-based measurements is valuable and applicable for monitoring/ assessing heart functionality changes after radiotherapy. In addition, it is substantioal and vital to assess the possible correlation with heart dose-volume histogram (DVH) parameters, in order to predict the incidence of ejection fraction variations on the basis of dose distribution in heart. Therefore, the aims of the current study were to investigate the effects of esophagus and left breast radiation therapy on the heart using echocardiography and to determine the relationship between dosimetric parameters and the ejection fraction due to radiotherapy.

MATERIALS AND METHODS

Patient population

The present study was conducted following the approval by Ethical Committee of Urmia University of Medical Sciences (Iran, approval number: IR.UMSU.REC.2017.89). Patients with esophageal (n=13, 40–90 years) and left breast cancer (n=21, 23–79 years), all of whom were referred to our radiotherapy center between March and October 2017, participated in the current study. All the patients were treated with radiotherapy, and 15 (esophagus=6 and breast cancer=9) received cisplatin as the chemotherapy drug (adjuvant therapy). The clinical and demographic characteristics of the studied patients are providedin table 1.

Table1. Clinical and demographic characteristics of the studied patients (n=34).

	Tumor site	
	Breast	**Esophagus**
Number of patients	21	13
Tumor stage (TNM• staging system)		
T1	5	4
T2	13	7
T3	3	2
Adjuvant therapy (CRT♦)	9	6
Radiotherapy	12	7
Smoking patients	2	4
Nonsmoking patients	19	9
Mean±SD*of age (years)	51.55±14	69.15±14
Mean±SD of blood pressure (mm Hg)	105.24±5.60	105.15±8.90
Mean±SD of fast blood sugar (mg/dL)	108.95±20.53	108.46±23.50
Mean±SD of cholesterol (mg/dL)	194.57±38.14	175.62±38.50
Mean±SD of weight (kg)	78.90±16.76	64±7.0
Mean±SD of height (cm)	162.71±4.74	164±6.0
Mean±SD ejection fraction (%)	55.95 ± 3.20	56.76±3.44

• TNM= Tumour Node and Metastasis ♦ Chemoradiotherapy (CRT) *SD= Standard Deviation

Informed consent was obtained from all participants. Echocardiography was performed on patients before starting radiotherapy. All the patients were treated with radiotherapy, and patients who had a heart problem before treatment or had undergone radiotherapy for another cancer in the chest area were excluded from the study. The following clinical and demographic factors were obtained from the patients' records in order to evaluate their association with the changes in the ejection fraction: age, weight, height, tumor stage, fast blood sugar, cholesterol, blood pressure, smoking, and alcohol.

Treatment planning

In this study, the CorePLAN treatment planning system (TPS), version 3.5.0.5 (Seoul C&J,Inc.), was used. CorePLAN is a commercial treatment planning system that uses photon and electron beam dose calculations for three-dimensional conformal radiation therapy (3D-CRT) [20, 21]. Dose calculations by CorePLAN were done through collapsed cone convolution (CCC) and equivalent tissue air ratio (ETAR) algorithms for photon, and the Hogstrom algorithm for electron beams. Numerous clinical tests have confirmed the accuracy of these algorithms [22, 23].

The methodology described in the IAEA TECDOC 1583 [24] was conducted using the CorePLAN treatment planning system. An anthropomorphic phantom was scanned with a computed tomography (CT), and treatment plans for different test cases were prepared on CorePLAN TPS [25]. Dose calculations were performed on CorePLAN TPS and measured with an ionization chamber, then differences between the calculated and measured doses were evaluted.

All the patients underwent CT scanning with a Siemens somatom system. After that, CT slices were transferred to a CorePLAN treatment planning system through a DICOM network. A radiation oncologist then contoured the gross tumor volume (GTV), the clinical target volume (CTV), the planning target volume (PTV), and the organs at risk (OARs) on the planning CT slices, in line with the guidelines of the International Commission on Radiation Units & Measurements (ICRU) [26, 27]. In all enrolled patients, PTV was defined as CTV +1cm margin.

All the patients were irradiated by a 6-MV photon beam from medical linear accelerator (Siemens Primus, Germany). The prescribed radiation doses for patients with breast and

esophageal cancers were 5000 cGy and 5040 cGy at 200 cGy per fraction respectively so that it covered at least 95% of the PTVs.

In the treatment planning system, the heart and lung of all the patients were contoured as OARs, and the following dosimetric parameters were extracted from TPS: PTV dose = dose received by planning target volume; Cadiac dose = dose received by the heart; V10, V20, V30, V40, and V50 are equal to the percent volume of heart receiving radiation doses of 10, 20, 30, 40, and 50 Gy, respectively; and NTCP = normal tissue complication probability. NTCP was calculated using the Lyman–Kutcher–Burman (LKB) model.

An example of contouring and dose distributions of three-dimensional conformal radiotherapy (3D-CRT) treatment plans in breast and esophagus cancer patients are shown in figure 1.

Evaluation of ejection fraction

The ejection fraction (EF) is the fraction of blood ejected from a ventricle of the heart with each heart beat. The ejection fraction is commonly measured by echocardiography, where the volumes of the heart's chambers are measured during the cardiac cycle. Prior to and six months after radiotherapy, echocardiography tests were obtained from the participants to evaluate the changes in the heart ejection fraction. Echocardiography was carried out with a GE Vivid S6 (GE-Healthcare, USA). Both echocardiography tests (before and after radiotherapy) were performed by a cardiologist to increase the accuracy of the study.

Statistical analysis

Statistical package for the Social Sciences (SPSS: version 20.0) was used for data analysis. To evaluate the normality distribution of the data, we analyzed the data using the Shapiro–Wilk test, which revealed that the data were not normally distributed. Therefore, the Wilcoxon non-parametric test was used to check the significance level of the results. The Wilcoxon non-parametric test was used to evaluate the relationship between the patients' cardiac ejection fraction before and six months after radiotherapy. In addition, the Pearson's correlation test was used to evaluate the relationship between dosimetric parameters and ejection fraction changes before and six months after radiotherapy.

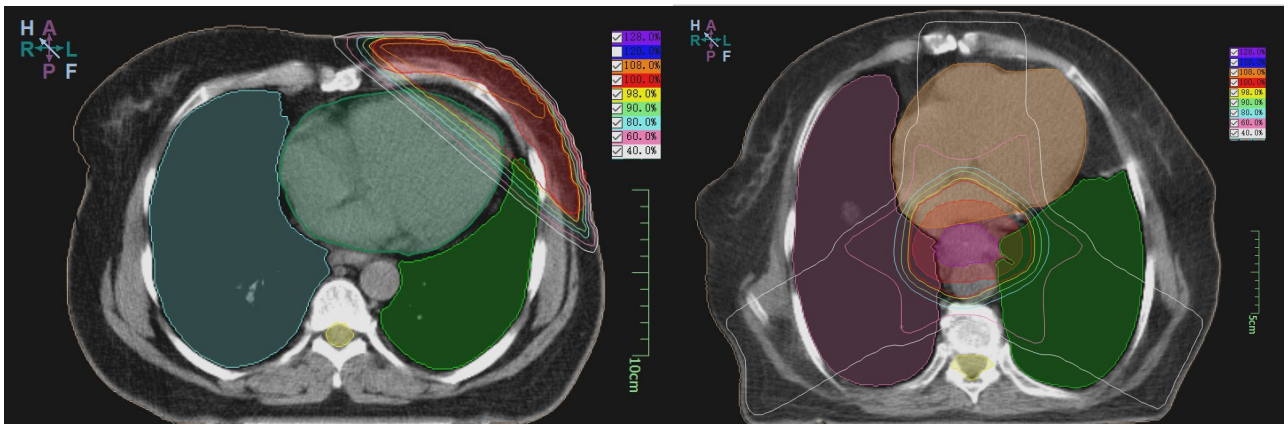

Figure 1. An example of contouring and dose distributions of the 3D-CRT treatment plans in breast **(left)** and esophagus **(right)** cancer patients.

RESULTS

A significant result of the clinical data was that a large number of patients with breast cancer had a Stage 2 tumor (table 1).

An example of dose-volume histograms (DVHs) of targets and OARs derived from the treatment plans of the 3D-CRT in breast and esophagus cancer patients are presented in figure 2.

Evaluation of the 3D-CRT treatment plans showed for patients with breast cancer, the

mean ± standard deviations of GTV and PTV were 23.50 ± 17.55 cm^3 and 207.90 ± 131.90 cm^3 respectively and also for patients with esophageal cancer, the mean ± standard deviations of GTV and PTV were 54.20 ± 27.78 cm^3 and 546.87±261.50 cm^3 respectively. The mean ± standard deviation of the delivered radiation dose to PTV for breast cancer patients was 5082.26 ± 167.38 cGy, and for esophagus cancer patients it was 5345.24±328.96 cGy. The mean ± standard deviations of the dosimetric parameters for the studied patients are provided in table 2.

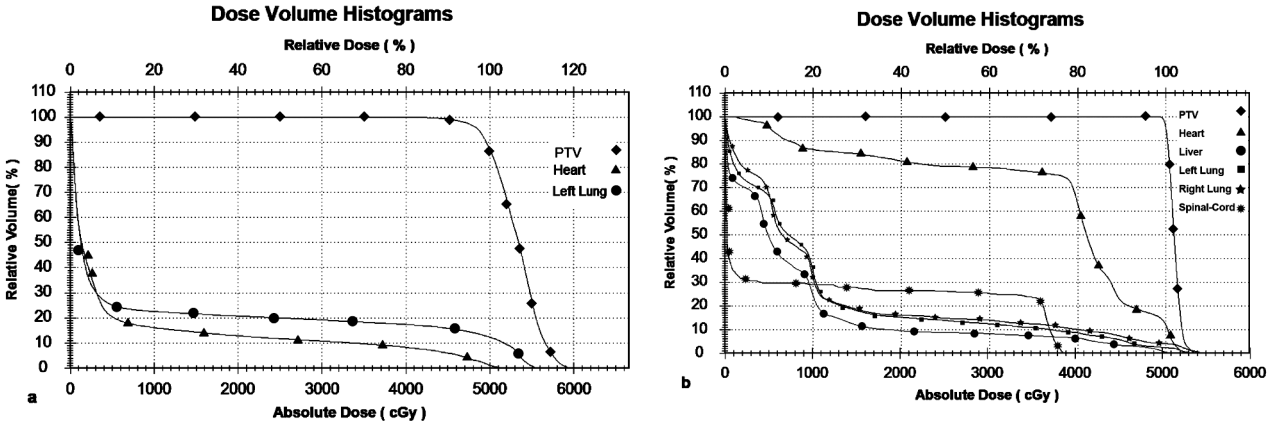

Figure 2. An example of dose-volume histograms (DVHs) of targets and OARs derived from the 3D-CRT treatment plans in breast **(a)** and esophagus **(b)** cancer patients.

Table 2. Mean ± standard deviations (SD) of dosimetry parameters for studied patients.

Dosimetric parameters	Breast	Esophagus
Mean±SD of PTV radiation dose (cGy)	5082.26±767.38	5345.24±328.96
Mean±SD of heart radiation dose (cGy)	617.32±265.95	2805.47±1111.74
V10(%)±SD	14.57±1.51	74.39±20.17
V20(%)±SD	10.94±1.39	62.80±21.14
V30 (%)±SD	8.49±1.15	52.84±22.32
V40 (%)±SD	5.96±0.86	43.44±19.87
V50 (%)±SD	1.026±0.91	13.70±10.13

The Wilcoxon non-parametric test was employed to evaluate the relationship between the patients' cardiac ejection fraction before and six months after radiotherapy. The mean ± standard deviations of the ejection fraction in the patients with breast cancer before and six months after treatment were 55.95% ± 3.20% and 53.10% ± 6.30% respectively, which were not statistically significant (P = 0.07). In patients with esophageal cancer, the mean ± standard deviations of pretreatment and post-treatment ejection fractions were 56.76%±3.44% and 52.09% ± 3.88% respectively. In patients with esophageal cancer, the ejection fraction difference between the pretreatment and the post-treatment was statistically significant (P = 0.005). To determine the association between the changes in the ejection fraction between smoking and non-smoking patients, the Mann–Whitney U test was conducted, but the results showed no significant difference (P=0.494).

The results of Pearson's correlation test between the dosimetric parameters of breast and esophageal 3D-CRT with ejection fraction changes are provided in table 3. This test results showed that in patients with breast cancer there was a statistically significant relationship between the amount of received radiation dose by the PTV and ejection fraction changes (P = 0.039). There was no statistically significant relationship between other dosimetric parameters and ejection fraction changes. This

test showed that in patients with esophageal cancer, there was a statistically significant relationship between the amount of received dose by the PTV and the ejection fraction changes (P = 0.001). Moreover, a statistically significant relationship was seen between (V30, V40, V50) and variations of the ejection fraction.

The mean ± standard deviations of NTCP obtained from the TPS for esophageal and breast cancer patients were 5.64% ± 3.23% and 6.19% ± 4.05% respectively.

Table 3. The results of Pearson's correlation test between the dosimetric parameters of breast and esophageal 3D-CRT with ejection fraction changes.

Dosimetric parameters	Pearson's correlation between dosimetric parameters and ejection fraction changes			
	Breast cancer treatment		Esophageal cancer treatment	
	r•	P-Value	r•	P-Value
PTV* radiation dose (cGy)	-0.454	0.039	-0.878	0.001
V10(%)	-0.213	0.353	-0.449	0.123
V20(%)	-0.251	0.273	-0.508	0.077
V30 (%)	-0.288	0.206	-0.760	0.003
V40 (%)	-0.293	0.198	-0.747	0.003
V50 (%)	-0.155	0.503	-0.566	0.044

* Planning Target Volume (PTV) • Correlation coefficients (r)

DISCUSSION

In the current study, we evaluated the effects of radiotherapy on the cardiac ejection fraction in breast and esophageal cancer patients. The results of our study showed an early variation of the ejection fraction in esophageal cancer patients who had received radiotherapy, while no significant changes were observed in breast cancer patients. Out of the 21 breast cancer patients who were studied, in five patients (24%) the ejection fraction decreased; in 14 patients (66%) the ejection fraction remained unchanged; and in two patients (10%) the ejection fraction increased. Out of the 13 patients with esophageal cancer, in eight (62%) the ejection fraction decreased and in five (38%) the ejection fraction remained unchanged.

Based on previous studies, the reduction in the ejection fraction after radiotherapy of esophageal cancer patients could be considered to cause long-term cardiac complications (8, 28). However, in the present study, six months after radiotherapy, the reduction in the cardiac ejection fraction was statistically significant (p=0.005). Since cardiac complications before 12 months after radiotherapy can be called acute complications (29), the reduction in the ejection fraction six months after radiotherapy is an acute complication of the heart.

During radiotherapy, when the heart receives a radiation dose, all cardiac structures can be damaged including myocardium, endocardium, nerve conducting pathways, pericardium, and coronary arteries (30, 31). The risk of these damages due to radiation is associated with the volume of the heart and the amount of radiation received by it. The radiation dose received by the PTV in both breast and esophageal cancer patients was approximately the same (table 2), but the volume of the heart that received radiation dose is important. We observed that the volume of the heart that received radiation dose (≥30Gy) in patients with esophageal cancer was higher than in breast cancer patients (table 2), this issue can be attributed to the reduction in the ejection fraction in patients with esophageal cancer.

The results of NTCP obtained from the TPS for both esophageal and breast cancer patients revealed that there was no significant correlation between the NTCP and the results obtained from the echocardiography test. In another study, a similar result was obtained, and no significant relationship was observed between the calculated NTCP and the clinical

findings regarding the ejection fraction (7).

In patients with esophageal cancer, there was a significant correlation between the variation of the ejection fraction and volume of heart receiving radiation doses ≥30 Gy (≥V30). Therefore, we suppose that the volume of heart receiving radiation dose 20 Gy (V20) maybe a useful dosimetric factor to avoid reduction in ejection fraction. Since in this study up to dose V30 the probability of developing heart complications is very low, heart V20 can be stated to be a decisive factor for 3D-CRT in the thoracic area.

In the current study, 19 patients were treated with radiotherapy and 15 patients received adjuvant therapy (CRT), i.e. cisplatin was used as a chemotherapy drug with radiation. According to the previous studies, cardiotoxicity following the administration of cisplatin may appear one year after treatment session (30, 32). Therefore, cardiotoxicity due to cisplatin cannot influence the results of our study.

A statistically significant decrease in the ejection fraction of esophageal cancer patients was observed, which revealed a significant correlation between the reduction in the ejection fraction and the volume of the heart that received a high dose (30, 40, and 50 Gy). This effect of radiotherapy may enhance the risk of post-treatment morbidity due to cardiac complications. Therefore, we suggest that, when it comes to treatment planning, the PTV should be carefully determined to reduce the size of dose reaching the heart. In patients with left-sided breast cancer, we did not see any significant change in the ejection fraction.

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REFERENCES

1. Hosseinzadeh M, Eivazi Ziaei J, Mahdavi N, Aghajari P, Vahidi M, Fateh A, *et al.* (2014) Risk factors for breast cancer in Iranian women: a hospital-based case-control study in tabriz, iran. *J breast cancer, **17**: 236-243.*
2. Ma NY, Cai XW, Fu XL, Li Y, Zhou XY, Wu XH, *et al.* (2014) Safety and efficacy of nimotuzumab in combination with radiotherapy for patients with squamous cell carcinoma of the esophagus. *Int J Clin Oncol, **19:** 297-302*.
3. Sadjadi A, Marjani H, Semnani S, Nasseri-Moghaddam S (2010) Esophageal cancer in Iran: A review. *Middle East J Cancer, **1**: 5-14*.
4. Lund M, von Döbeln GA, Nilsson M, Winter R, Lundell L, Tsai JA, *et al.* (2015) Effects on heart function of neoadjuvant chemotherapy and chemoradiotherapy in patients with cancer in the esophagus or gastroesophageal junction–a prospective cohort pilot study within a randomized clinical trial. *Radiother Oncol, **10**: 16*.
5. Bouillon K, Haddy N, Delaloge S, Garbay JR, Garsi JP, Brindel P, *et al.* (2011) Long-term cardiovascular mortality after radiotherapy for breast cancer. *J American Coll Cardiol, **57**: 445-452*.
6. Correa CR, Litt HI, Hwang WT, Ferrari VA, Solin LJ, Harris EE, *et al.* (2007) Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. *J Clin Oncol, **25**: 3031-3037*.
7. Tripp P, Malhotra H, Javle M, Shaukat A, Russo R, De Boer S, *et al.* (2005) Cardiac function after chemoradiation for esophageal cancer: comparison of heart dose-volume histogram parameters to multiple gated acquisition scan changes. *Dis Esophagus, **18**: 400-405*.
8. Mukherjee S, Aston D, Minett M, Brewster AE, Crosby TD (2003) The significance of cardiac doses received during chemoradiation of oesophageal and gastro–oesophageal junctional cancers. *Clin Oncol (R Coll Radiol), **15**: 115-120*.
9. Hatakenaka M, Yonezawa M, Nonoshita T, Nakamura K, Yabuuchi H, Shioyama Y, *et al.* (2012) Acute cardiac impairment associated with concurrent chemoradiotherapy for esophageal cancer: magnetic resonance evaluation. *Int J Radiat Oncol Biol Phys, **83**: e67 -e73*.
10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr, **28(1):** 1-39.e14.*
11. Shirai K, Tamaki Y, Kitamoto Y, Murata K, Satoh Y, Higuchi K, *et al.* (2011) Dose–volume histogram parameters and clinical factors associated with pleural effusion after chemoradiotherapy in esophageal cancer patients. *Int J Radiat Oncol Biol Phys, **80**: 1002-1007*.
12. Martel MK, Sahijdak WM, Ten Haken RK, Kessler ML, Turrisi AT (1998) Fraction size and dose parameters

related to the incidence of pericardial effusions. *Int J Radiat Oncol Biol Phys,* ***40****: 155-161*.
13. Fukada J, Shigematsu N, Takeuchi H, Ohashi T, Saikawa Y, Takaishi H, *et al.* (2013) Symptomatic pericardial effusion after chemoradiation therapy in esophageal cancer patients. *Int J Radiat Oncol Biol Phys,* ***87****: 487-493*.
14. Canney P, Sanderson R, Deehan C, Wheldon T (2001) Variation in the probability of cardiac complications with radiation technique in early breast cancer. *Br J Radiol,* ***74****: 262-265*.
15. Nellessen U, Zingel M, Hecker H, Bahnsen J, Borschke D (2010) Effects of radiation therapy on myocardial cell integrity and pump function: which role for cardiac biomarkers? *Chemotherapy* ***56****: 147-152*.
16. Marín J, Marín E, Gutiérrez-Iñiguez MA, Avendaño C, Rodríguez-Martínez MA (2000) Mechanisms involved in the hemodynamic alterations in congestive heart failure as a basis for a rational pharmacological treatment. *Pharmacol Ther,* ***88****: 15-31*.
17. Brenner DJ, Elliston CD, Hall EJ, Berdon WE (2001) Estimated risks of radiation-induced fatal cancer from pediatric CT. *AJR Am J Roentgenol,* ***176****: 289-296*.
18. Rehani MM, Bongartz G, Kalender W, Golding SJ, Gordon L, Murakami T, *et al.* (2000) Managing patient dose in computed tomography. *Ann ICRP,* ***30****: 7-45*.
19. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, *et al.* (2014) 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. *Eur Heart J Cardiovasc Imaging,* ***15****: 1063-1093.*
20. Nasrollah J, Mikaeil M, Omid E, Mojtaba SS, Ahad Z (2014) Influence of the intravenous contrast media on treatment planning dose calculations of lower esophageal and rectal cancers. *J Cancer Res Ther,* ***10****: 147-152*.
21. Molazadeh M, Saberi H, Rahmatnezhad L, Molani A, Jabbari N (2013) Evaluation The Effect Of Photon Beam Energies On Organ At Risk Doses In Three-Dimensional Conformal Radiation Therapy. *Res J App Sci Eng Technol,* ***6****: 2110-2117*.
22. Mackie T, Scrimger J, Battista J (1985) A convolution method of calculating dose for 15-MV X-rays. *Med Phys,* ***12****: 188-196*.
23. Ahnesjö A (1989) Collapsed cone convolution of radiant energy for photon dose calculation in heterogeneous media. *Med Phys, 16: 577-592*.
24. IAEA (International Atomic Energy Agency) (2008) Commissioning of radiotherapy treatment planning systems: testing for typical external beam treatment techniques. Vienna: IAEA, TECDOC 1583.
25. Mahmoudi R, Jabbari N, Aghdasi M, Khalkhali HR (2016) Energy Dependence of Measured CT Numbers on Substituted Materials Used for CT Number Calibration of Radiotherapy Treatment Planning Systems. *PLoS One,* ***8;11 (7)****: e0158828*.
26. International Commission on Radiation Units and Measurements (1999) Prescribing, Recording, and Reporting Photon Beam Therapy (supplement to ICRU Report 50). ICRU Report 62. Bethesda, MD. International Commission of Radiation Units and Measurements.
27. Wambersie A and Landgerg T (1999) ICRU report 62: prescribing, recording and reporting photon beam therapy. ICRU Publ Bethesda MD.
28. Savage DE, Constine LS, Schwartz RG, Rubin P (1990) Radiation effects on left ventricular function and myocardial perfusion in long term survivors of Hodgkin's disease. *Int J Radiat Oncol Biol Phys,* ***19****: 721-727*.
29. Galderisi M, Marra F, Esposito R, Lomoriello VS, Pardo M, de Divitiis O (2007) Cancer therapy and cardiotoxicity: the need of serial Doppler echocardiography. *Cardiovasc Ultrasound,* ***5****: 4*.
30. Rodemann HP and Bamberg M (1995) Cellular basis of radiation-induced fibrosis. *Radiother Oncol,* ***35****: 83-90*.
31. Sporn LA, Rubin P, Marder V, Wagner D (1984) Irradiation induces release of von Willebrand protein from endothelial cells in culture. *Blood,* ***64****: 567-570*.
32. Meinardi MT, Gietema JA, van der Graaf WT, van Veldhuisen DJ, Runne MA, Sluiter WJ, *et al.* (2000) Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. *J Clin Oncol,* ***18****: 1725-1732*.