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Original Article

Assessment of Cardiac Autonomic Functions by Heart Rate Recovery Indices in Patients Receiving Chest Radiotherapy

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ABSTRACT

Objective: Although the introduction of radiation therapy for the management of thoracic malignancies has led to a significant improvement in disease-specific survival, this has resulted in the emergence of a new spectrum of cardiovascular disorders induced by radiation injury. Heart rate recovery, as a predictor of cardiovascular events and an indicator of autonomic functions, is measured non-invasively and easily. In the present study, we investigated the effects of mediastinal radiotherapy on heart rate recovery parameters.

Methods: Twenty-one patients were included in this study who were planned to receive chest radiotherapy because of lymphoma or lung cancer. Heart rate recovery parameters were evaluated by treadmill exercise before and after radiotherapy.

Results: We have found decrease in heart rate recovery parameters (26.05 ± 12.54 vs. 19.52 ± 12.28 for HRR1, 39.1 ± 16.15 vs. 32.86 ± 14.83 for HRR2, 42.81 ± 17.66 vs. 38.05 ± 16.14 for HRR3). The higher doses of mediastinal radiotherapy caused significant changes on heart rate recovery parameters. HRR1 changed from 25.70 ± 15.12 to 22.00 ± 14.38 in low dose group and from 26.36 ± 10.41 to 17.27 ± 10.10 in high-dose group ($P < .05$). Attenuation of HRR2 and HRR3 were also more evident in high mediastinal dose group ($P < .05$).

Conclusion: Heart rate recovery parameters were decreased especially in patients who were exposed to more intense mediastinal radiation.

Keywords: cardiac autonomic functions, heart rate recovery, lung cancer, lymphoma, Radiotherapy

INTRODUCTION

Advances in cancer treatment have resulted in a significant improvement in survival in many types of cancer. However, considerable exposure of cardiovascular structures to radiation has been shown to result in cardiovascular adverse effects in the long term.[1] Risk factors for cardiotoxicity associated with radiation therapy include a radiation dose greater than 30 Gy or 2 Gy/fraction, a large volume of cardiovascular structures within the irradiated field, younger age at exposure, a long period following exposure, adjuvant chemotherapy, and co-morbidities (such as diabetes mellitus, hypertension, any other cardiovascular disease).[2] Patients receiving thoracic irradiation for Hodgkin's lymphoma, breast cancer, and lung cancer have risk for cardiovascular adverse effects.[1,3]

Heart rate recovery (HRR) is a relatively inexpensive and very simple diagnostic and prognostic tool that reflects the cardiac autonomic functions, which can be applied in various clinical settings.[4] Heart rate recovery indices show the rate of decline in the heart rate (HR) after the cessation of exercise test and it is defined HR difference between the maximal HR on exercise and the HR during the recovery phase. HRR after graded exercise reflects autonomic activity and predicts cardiovascular events and mortality in various systemic disorders.[4,5]

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Although detection of unfavorable effects of radiotherapy on cardiovascular system in short term may have been beneficial, most adverse effects are noticed in the long-term follow-up. In this study, we aimed to investigate whether thoracic irradiation due to Hodgkin's lymphoma or lung cancer may have an impact on cardiac autonomic functions evaluated with HRR.

METHODS

Among patients who presented to the radiation oncology department between March 2013 and November 2013, 21 patients who were scheduled for mediastinal radiotherapy for lung cancer or lymphoma, in which irradiation field included the heart, were included in the study. Baseline demographic, clinical, and echocardiographic parameters were recorded. Patients underwent detailed physical examination and measurements including height and body weight were obtained. If present, adjuvant chemotherapy was also recorded.

Patients with a history of coronary artery disease, peripheral artery disease, heart failure (left ventricular ejection fraction <50%), acute coronary syndrome, acute or chronic kidney disease, severe valvular heart disease, uncontrolled hypertension, uncontrolled diabetes, and vasculitis were excluded. Furthermore, active smokers and patients with contraindication for exercise stress test were also not included.

Standard 12-lead electrocardiography and transthoracic echocardiography were obtained from all patients. Exercise stress test was performed for evaluation of heart rate recovery at baseline and on the 15th day following radiotherapy.

Blood samples were obtained via the antecubital vein in sterile conditions from the patients during the computer-optimized treatment planning period. Results of routine laboratory tests, including complete blood cell count and serum biochemistry, were recorded.

Three-dimensional conformal radiation therapy was performed in the radiation oncology department. An accurate radiation dose calculation was made. Radiation exposure doses of the left ventricle, right atrium involving sinoatrial node, and paravertebral region involving the autonomic ganglia were determined besides the mediastinal dose. Doses lower than the median dose for each region were defined as low dose of radiation, whereas doses higher than (or equal to) the median dose were defined as high dose. Patients received treatment in the linear accelerator device. Mean radiation doses the patients received throughout the therapy were determined in the treatment planning program.

All patients were subjected to exercise stress test using the modified Bruce protocol. 12- lead electrocardiography was recorded at the standard speed of 25 mm/sec during the test. Minimum exercise test duration of 6 minutes and maximal heart rate of 85% of age-predicted maximal heart rate (220- age) were targeted. Maximal exercise was followed by rest phase which lasted at least 3 minutes. Heart rate at maximal exercise; first, second, and third minute of the recovery was noted. HRR1, 2, and 3 were defined as the subtraction of heart rate at maximal exercise from heart rate at the first, second, and third minutes of the recovery phase, respectively.

The study was approved by the ethics committee of Hacettepe University (Date: March 27, 2013, Decision no: GO 13/ 215- 22) and was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Statistical Analysis

Statistical analysis was made using Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, Ill, USA) and Medcalc 11.4.2 (MedCalc Software, Mariakerke, Belgium). Shapiro–Wilk test was used to test the normality of the study population. Numerical variables were expressed as mean ± standard deviation or median (interquartile range, defined as minimum-maximum). Categorical variables were represented as number and frequency. Comparing differences between 2 independent groups when the dependent variable was either ordinal or continuous, but rather normally or non-normally distributed, was done using *t*-test or Mann–Whitney *U* test, respectively. Categorical variables were compared using chi-square or Fisher's exact chi-square test. Differences between before and after radiotherapy were evaluated with paired sample's *t*-test for normally distributed parameters and Wilcoxon signed-rank test for non-normally distributed parameters. Post-hoc analyses regarding the contribution of adjuvant chemotherapy and radiation dose on differences in parameters following radiotherapy, two-way analysis of variance test was done in paired samples. A P value <.05 was considered statistically significant.

Main Points

- Considerable exposure of cardiovascular structures to radiation has been shown to result in cardiovascular adverse effects.
- Heart rate recovery (HRR) is a relatively inexpensive and very simple diagnostic and prognostic tool that reflects the cardiac autonomic functions and predicts cardiovascular events and mortality in various conditions.
- Reduce in HRR is significantly more prominent in higher mediastinal radiation dose when compared to lower irradiation dose.

RESULTS

Twenty-one patients (51.6 ± 16.0 years, 61.9% male) were included in the study. Eight patients (38.1%) were scheduled for radiotherapy for treatment of lymphoma, whereas the remaining 13 patients (61.9%) were being treated for lung cancer. Only 2 patients (9.5%) had a history of hypertension and diabetes mellitus as cardiovascular risk factors. Four patients (19.0%) received adjuvant chemotherapy. Specifically, 1 patient received carboplatin, 2 patients received carboplatin + paclitaxel, and 1 patient received cisplatin + etoposide. Baseline demographic, clinical, and echocardiographic characteristics of the patients are shown in Table 1.

Table 1. Baseline Characteristics of the Patients (n=21)

Age	51.57 ± 16.01
Gender	
Female (n, %)	8 (38.1)
Male (n, %)	13 (61.9)
Disease	
Lymphoma (n, %)	8 (38.1)
Lung cancer (n, %)	13 (61.9)
BMI (kg/m^2)	27.32 ± 4.91
Hypertension (n, %)	2 (9.5)
Diabetes mellitus (n, %)	2 (9.5)
Drugs	
Beta blockers (n, %)	2 (9.5)
ACE-İnh/ARB (n, %)	1 (4.8)
Echocardiography	
LVEF (%)	61.38 ± 3.79
LVEDD (mm)	46.57 ± 3.41
Adjuvant chemotherapy	
Non-receivers (n, %)	17 (81.0)
Receivers (n, %)	4 (19.0)

When baseline characteristics of the patients were evaluated regarding the type of malignancy, only age and prevalence of adjuvant chemotherapy significantly differed between groups. Patients diagnosed with lung cancer were older [median 62 (40-68) vs. 31 (20-60) years, *P* = .006]. Adjuvant chemotherapy was seen only in patients with lung cancer (*P* = .036).

None of the blood pressure parameters, including systolic, diastolic, and mean blood pressure and pulse pressure, showed significant change following radiotherapy A statistically significant change did not occur in heart rate, central systolic, and diastolic blood pressure values following radiotherapy (*P* > .05).

Maximal heart rate (153.4 ± 19.9 vs. 145.4 ± 16.5 bpm, *P* = .001), HRR1 (26.1 ± 12.5 vs. 19.5 ± 12.3 bpm, *P* = .001), HRR2 (39.1 ± 16.2 vs. 32.9 ± 14.8 bpm, *P* = .002) and HRR3 (42.8 ± 17.7 vs. 38.1 ± 16.1 vs., *P* = .042) parameters were found to be significantly lowered following radiotherapy. However, this was not persistent following the consideration of the forementioned possible confounders (*P* > .05). When heart rate recovery parameters were evaluated regarding presence of adjuvant chemotherapy, only HRR1 was significantly lower in patients who received adjuvant chemotherapy (22.8 ± 10.4 vs. 34.5 ± 8.2 bpm, *P* = .046). Heart rate recovery parameters before and after radiotherapy is shown in Table 2 and Figure 1.

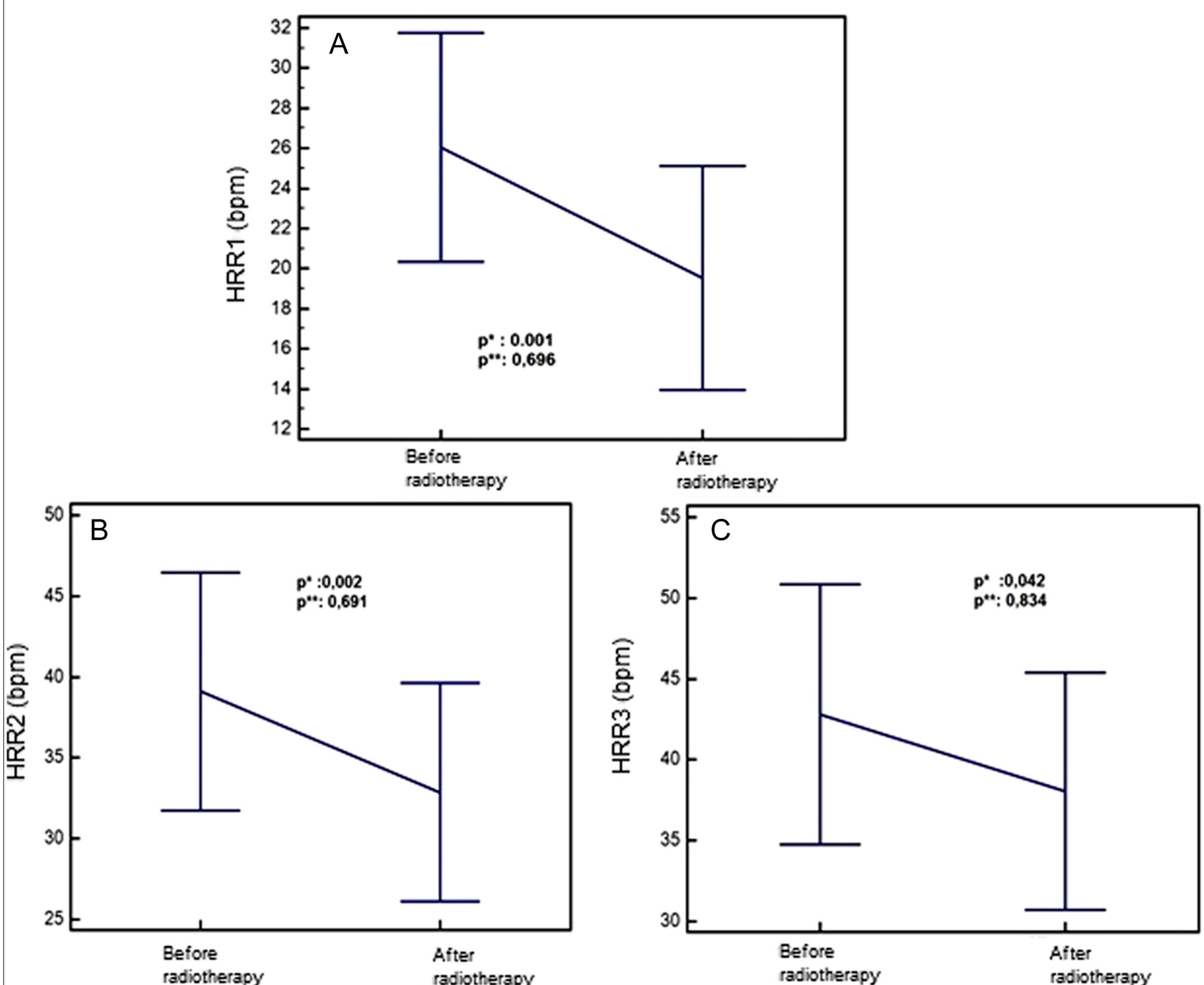
The median radiation doses for mediastinum, left ventricle, atrium, and paravertebral region were 40 Gy, 20 Gy, 30 Gy, and 30 Gy, respectively. Patients who received high-dose radiation to the mediastinum were found to have greater decrease in HRR1 (−9.1 vs. −3.7 bpm *P* = .001), HRR2 (−9.2 vs. −3.0 bpm *P* = .003) and HRR3 (−8.5 vs. −0.6 bpm *P* = .002) when compared to those who received low-dose radiation (Figure 2). Heart rate recovery parameters did not significantly differ between low and high-dose radiation exposure in regions other than mediastinum (*P* > .05). Heart rate recovery parameters regarding irradiation site are shown in Table 3.

Table 2. Heart Rate Recovery Parameters Before and After Radiotherapy (n=21)

	Before Radiotherapy	After Radiotherapy	*P**	*P***
Maximal heart rate (bpm)	153.4 ± 19.9	145.4 ± 16.5	.001*	.518
Maximal heart rate-adjuvant chemotherapy (bpm)			.876	.437
Non-recipient (n=17)	154.5 ± 21.9	146.7 ± 18.1		
Recipient (n=4)	148.8 ± 4.9	140.0 ± 5.7		
HRR1 (bpm)	26.1 ± 12.5	19.5 ± 12.3	.001*	.696
HRR1-adjuvant chemotherapy (bpm)			.046*	.046*
Non-recipient (n=17)	24.1 ± 12.7	18.8 ± 12.9		
Recipient (n=4)	34.5 ± 8.2	22.8 ± 10.4		
HRR2 (bpm)	39.1 ± 16.2	32.9 ± 14.8	.002*	.691
HRR2-adjuvant chemotherapy (bpm)			.341	.232
Non-recipient (n=17)	37.5 ± 16.6	32.3 ± 14.7		
Recipient (n=4)	45.8 ± 14.1	35.3 ± 17.4		
HRR3 (bpm)	42.8 ± 17.7	38.1 ± 16.1	.042*	.834
HRR3-adjuvant chemotherapy (bpm)			.299	.240
Non-recipient (n=17)	41.8 ± 18.4	38.2 ± 16.3		
Recipient (n=4)	47.0 ± 15.7	37.3 ± 18.1		

*No interaction was taken into account during the analysis.
**Beta-blockers and type of malignancy were taken into consideration during analysis.
HRR1 heart rate recovery at first minute; HRR2 heart rate recovery at second minute; HRR3 heart rate recovery at third minute.

Figure 1. Comparison of heart rate recovery (HRR) parameters. HRR1 (A), HRR2 (B), and HRR3 (C) show first, second, and third minute HRR parameters, respectively. *No interaction was taken into account during analysis.**Beta-blockers and type of malignancy were taken into consideration during analysis.



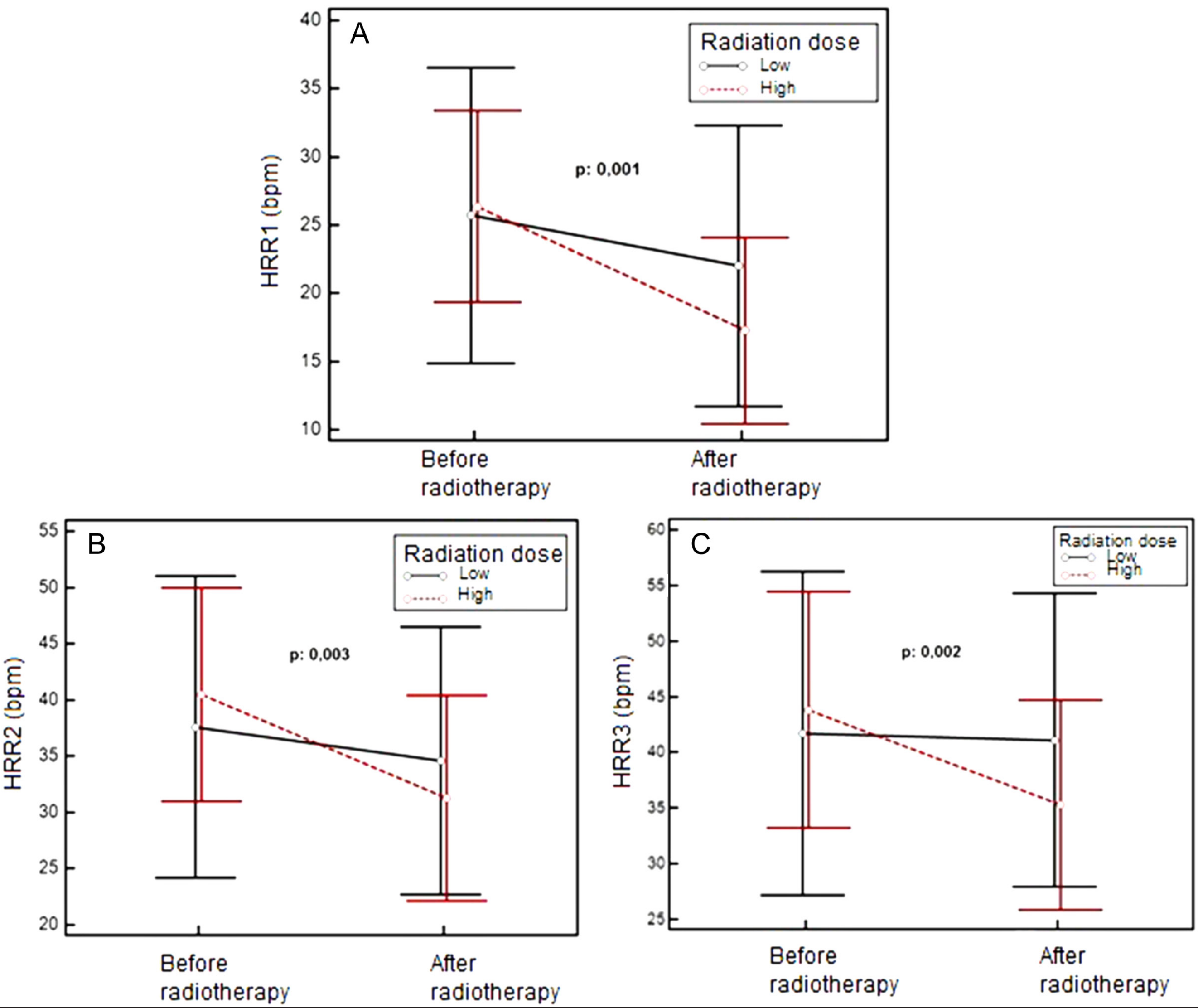
DISCUSSION

This study investigates the impact of thoracic irradiation for Hodgkin's lymphoma or lung cancer on cardiac autonomic function parameters in short term. We investigated the unfavorable effects of radiation therapy by heart rate recovery in short-term follow- up of 15 days.

Abnormal HRR, which is due to sympathetic withdrawal, parasympathetic reactivation, or both, has been reported to be an independent predictor of mortality in previous studies.[6,7] The decline in HR during recovery is principally due to a reactivation of the parasympathetic nervous system, mostly in the early recovery period.[8,9] Inadequate decline in HR immediately after exercise, reflects reduced parasympathetic nervous system activity and this is defined as an attenuated HRR.[10,11] Kannankeril et al[12] demonstrated that sympathetic withdrawal also contributes significantly to early HRR. they suggested that abnormal HRR might be attributable to a defect in sympathetic withdrawal and parasympathetic reactivation or both of them. As these changes correlate with increased risk of death, it was hypothesized that an attenuated HRR would similarly predict an increased risk of death.[7] Cole et al[13] showed that A delayed decrease in the heart rate during the first minute after graded exercise is a powerful predictor of overall mortality, independent of workload, the presence or absence of myocardial perfusion defects, and changes in heart rate during exercise.

However, there is limited data on the impact of cancer treatment on cardiac autonomic functions and most of the data relies on small study population.[13-16] Recently, thoracic radiotherapy has been reported to be associated with autonomic dysfunction, as measured by elevated resting heart rate and abnormal HRR in 263 Hodgkin's lymphoma survivors at a median follow-up of 19 years when compared to control subjects.[17] These

Figure 2. Figure demonstrating the relationship between mediastinal radiation dose and heart rate recovery (HRR). HRR1 (A), HRR2 (B), and HRR3 (C) show first, second, and third minute HRR parameters, respectively.



abnormalities were found to be associated with impaired exercise tolerance, and abnormal HRR predicted increased all-cause mortality in radiotherapy patients.[17]

Our study has demonstrated that HRR1, HRR2, and HRR3 were significantly reduced following radiotherapy. However, when confounding factors were taken into account, this statistical significance was lost ($P > .05$).

When HRR parameters were analyzed regarding the radiation dose, interesting results were obtained. Reduce in HRR1, HRR2, and HRR3 were significantly more prominent in higher mediastinal radiation doses when compared to lower irradiation doses.

Despite autonomic function parameters were expected to be affected by radiation applied at the paravertebral region and atria, no significant effect was observed between radiation dose applied at paravertebral region and atria and HRR.

It is already known that the risk of cardiovascular death is increased following radiotherapy for cancer.[18] At 25 years of follow-up, Schellong et al[19] determined 21% of cumulative cardiac disease incidence in patients with Hodgkin's disease who received mediastinal radiotherapy at the dose of 36 Gy. This risk was reduced to 6% and 5% with doses of 25 Gy and 20 Gy, respectively. Literature data show increased cardiac disease risk with higher mediastinal doses than 30-35 Gy.[20,21]

CONCLUSION

However, since effects related to radiotherapy mostly develop within more than 10 years, studies with short-term follow-up may be insufficient to demonstrate significant cardiovascular

Table 3. Heart Rate Recovery Parameters Regarding Irradiation Site (n=21)

	Irradiation Site	Irradiation Dose	Before Radiotherapy	After Radiotherapy	*P*
Maximal heart rate (bpm)	**Mediastinum**	**Low**	161.4 ± 24.8	153.5 ± 18.8	.696
		High	146.2 ± 10.6	138.0 ± 10.2	
	Left ventricle	**Low**	147.5 ± 16.5	140.1 ± 13.7	.897
		High	158.8 ± 21.8	150.2 ± 18.0	
	Atrium	**Low**	155.5 ± 19.0	146.0 ± 19.5	.580
		High	151.6 ± 21.3	144.8 ± 14.3	
	Paravertebral region	**Low**	160.2 ± 23.2	150.7 ± 20.9	.520
		High	150.7 ± 18.6	143.3 ± 14.8	
HRR1 (bpm)	**Mediastinum**	**Low**	25.7 ± 15.1	22.0 ± 14.4	.001
		High	26.4 ± 10.4	17.3 ± 10.1	
	Left ventricle	**Low**	26.5 ± 15.5	21.8 ± 15.1	.410
		High	25.6 ± 10.0	17.5 ± 9.4	
	Atrium	**Low**	27.4 ± 14.1	21.0 ± 15.3	.627
		High	24.8 ± 11.5	18.2 ± 9.3	
	Paravertebral region	**Low**	27.5 ± 12.0	19.3 ± 14.5	.288
		High	25.5 ± 13.1	19.6 ± 11.9	
HRR2 (bpm)	**Mediastinum**	**Low**	37.6 ± 18.8	34.6 ± 16.6	.003
		High	40.5 ± 14.1	31.3 ± 13.6	
	Left ventricle	**Low**	37.6 ± 19.0	33.4 ± 17.4	.734
		High	40.5 ± 13.8	32.4 ± 12.9	
	Atrium	**Low**	38.5 ± 17.6	31.7 ± 16.1	.664
		High	39.6 ± 15.6	33.9 ± 14.3	
	Paravertebral region	**Low**	43.0 ± 15.8	33.8 ± 18.5	.706
		High	37.5 ± 16.6	32.5 ± 13.9	
HRR3 (bpm)	**Mediastinum**	**Low**	41.7 ± 20.3	41.1 ± 18.4	.002
		High	43.8 ± 15.8	35.3 ± 14.1	
	Left ventricle	**Low**	41.2 ± 21.0	37.3 ± 18.7	.796
		High	44.3 ± 15.0	38.7 ± 14.3	
	Atrium	**Low**	43.2 ± 19.8	37.4 ± 18.4	.720
		High	42.5 ± 16.5	38.6 ± 14.7	
	Paravertebral region	**Low**	49.3 ± 17.3	40.7 ± 20.5	.697
		High	40.2 ± 17.7	37.0 ± 14.8	

HRR1 heart rate recovery at first minute; HRR2 heart rate recovery at second minute; HRR3 heart rate recovery at third minute.

mortality or morbidity data. Our study is remarkable for the fact that unfavorable effects of radiation therapy have been demonstrated in short-term follow-up of 15 days. Early detection of associated subclinical changes may be beneficial for the long-term follow-up and risk stratification.

There are some limitations of our study. First, a larger study population may render the results more reliable. Second, studies with longer follow-up periods are necessary to reveal the long-term effects of radiotherapy. Third, calculation of radiation dose exposure of mediastinal structures separately may help identify the specific effects of mediastinal structures on cardiovascular endpoints. Finally, our study is a single-center study. Randomized multi-center studies are necessary to further clarify the outcomes of thoracic irradiation on cardiovascular outcomes.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Hacettepe University, (Date: March 27, 2013, Decision no: GO 13/ 215- 22).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Author Contributions: Concept – S.G.F., E.B.K., H.Y., M.C., K.A.; Supervision – E.B.K., M.L.S., K.A., M.C.; Materials – S.G.F., E.H., N.M., G.Y.; Data Collection and/or Processing – S.G.F., E.H., N.M., D.K., G.Y.; Analysis and/or Interpretation – S.G.F., D.K., G.Y., M.L.S., H.Y., A.H.A.; Literature Review – S.G.F., E.B.K., A.H.A., M.L.S., H.Y.; Writing – S.G.F., D.K., E.H., N.M., Critical Review – H.Y., M.L.S., A.H.A., M.C., K.A.

Declaration of Interests: The authors declare that they have no competing interest.

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